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(54) FUSED PYRIDAZINE COMPOUND

KONDENSIERTE PYRIDAZINVERBINDUNGEN

COMPOSE DE PYRIDAZINE CONDENSE

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Description

Field of the Invention

[0001] The present invention relates to a novel fused pyridazine compound. In particular, the present invention relates to a novel fused pyridazine compound which is useful as drug.

Description of Related Background Art

[0002] Recently, studies on compounds exhibiting inhibitory activity against cyclic GMP phosphodiesterase (hereinafter referred to as "cGMP-PDE") have proceeded and attempts have been made to apply such compounds to the prevention and treatment of circulatory failures such as hypertension, angina pectoris and myocardial infarct.

[0003] Known examples of the compound usable in the prevention and treatment of circulatory failures include quinazoline compounds disclosed in JP-A-29582/1975, 4H-3,1-benzoxazin-4-one compounds disclosed in WO 88/09790, 1H-2,3,4,5-tetra-hydroimidazo[2,1-b]quinazolin-2-one and 1',2,3,4,5,6-hexahydropyrimido[2,1-b]quinazolin-2-one disclosed in JP-A-86894/1973, nitrogenous heterocyclic compounds disclosed in WO 93/07124 and 4-aminoquinazoline derivatives disclosed in EP 579496.

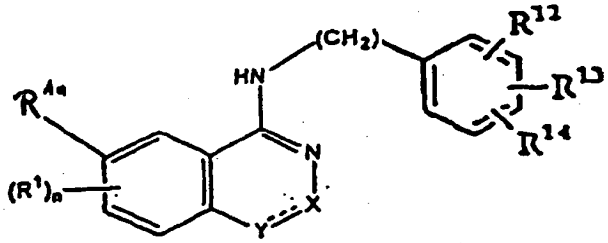
[0004] However, most of the compounds described above are not on the market and many of them have problems of solubility, in vivo dynamics and toxicity which must be solved prior to the use as drugs.

[0005] The use of phosphonic acid derivatives for the treatment of hyperlipemia which is a stage precedent to ischemic heart diseases such as myocardial infarction was disclosed in WO 94/20508. Pyridazine derivatives with platelet agglutination inhibitory effects were disclosed in EP 0 449 203 as well as in EP 0 534 443. Pyridazino pyridazines have been described in US 3 494 921. They turned out to be useful as pesticides and for the treatment of the nervous system of animals. In JP 2129180 phthatazine derivatives were disclosed as antithrombotic agents with high safety capable of oral and parenteral administrations. The synthesis of pyridazine derivatives condensed with a heterocycle was described by K. Körmendy et al. in *Acta Chim. Hung.*, **112**, 487 - 499 (1983). Medical studies were not revealed by his group. None of these documents, however, discloses pyridazine derivatives with anti cGMP-PDE activity. As a second messenger, cGMP has several functions, apart from those in regulation of thrombocyte aggregation. Moreover, it was a further object of the invention to disclose substances with a considerable pulmonary arterial pressure (PAP) lowering activity.

Disclosure of the Invention

[0006] Under the above circumstances, the inventors of the present invention have started their studies for the purpose of finding a compound which exhibits an excellent cGMP-PDE inhibiting activity, has such a high water solubility as to be well absorbed into the living body, and is less toxic.

[0007] As a result of the studies, they have found that the above object can be attained by a fused pyridazine compound represented by the following general formula (I) or a pharmacologically acceptable salt thereof. The present invention has been accomplished on the basis of this finding.



(I)

wherein

n is an integer of 1 to 3:
R^1 represents a hydrogen atom, a halogen atom, a nitro group, an amino group, a cyano group or a 4-hydroxypiperidin-1-yl group; R^{1a} represents a halogen atom, a nitro group, an amino group, a cyano group or a 4-hydroxypiperidin-1yl group;

R^{12}, R^{13} and R^{14} represent each independently hydrogen. halogen; optionally substituted lower alkyl or optionally substituted lower alkoxy, or alternatively two of R^{12}, R^{13} and R^{14} which are bonded to the carbon atoms adjacent to each other may be united to form methylenedioxy or ethylenedioxy ;
--- represents a single bond or a double bond, and

(1) when the above bond is a double bond;
then X represents a nitrogen atom, and Y represents a =C-B group, wherein B represents a halogen atom, a group represented by the formula NR^7R^8, wherein R^7 represents hydrogen, or lower alkyl and R^8 represents lower alkyl optionally substituted by hydroxy, carboxy or pyridyl, or alternatively R^7 and R^8 together with the nitrogen atom to which they are bound form a ring which may be substituted; a lower alkoxy group or a lower hydroxyalkoxy group;
(2) when the above bond is a single bond,
then X represents a $>NR^6$ groups wherein R^6 represents hydrogen or lower alkyl optionally substituted by a hydroxyl group, a carboxyl group, an acyl group or a tetrahydropyranyl group; and
Y represents a carbonyl group;
provided that B is not Cl, when R^1 is 7- or 8-nitro and R^{12} and R^{13} are 3,4-methylenedioxy and R^{14} is hydrogen.

[0008] In the above definition of the general formula (I), the lower alkyl group constituting the optionally substituted lower alkyl as defined with respect to R^6, R^7, R^8, R^{12}, R^{13} and R^{14} may be a linear or branched lower alkyl group having 1 to 6 carbon atoms. and examples thereof include methyl. ethyl, n-propyl, isopropyl, n-butyl, isobutyl. 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl. The substituent constituting it includes with respect to R^{12}, R^{13} and R^{14} a hydroxyl group, a nitro group, an amino group, a cyano group, acyl groups such as an acetyl group and a benzoyl group; lower alkoxy groups such as a methoxy group and an ethoxy group; halogen atoms such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom; and an optionally protected carboxyl group. One or more of these substituents may be bonded to one or more carbon atoms of the lower alkyl group.

[0009] The lower alkoxy group constituting the lower alkoxy group as defined with respect to R^{12}, R^{13}, R^{14} and B may be one derived from the above lower alkyl group, and examples thereof include a methoxy group, an ethoxy group and a propoxy group.

[0010] The optional substituent constituting it with respect to R^{12}, R^{13} and R^{14} includes a hydroxyl group, a nitro group, an amino group, a cyano group, acyl groups such as an acetyl group and a benzoyl group; lower alkoxy groups such as a methoxy group and an ethoxy group; halogen atoms such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom; and an optionally protected carboxyl group. One or more of these substituents may be bonded to one or more carbon atoms of the lower alkoxy group.

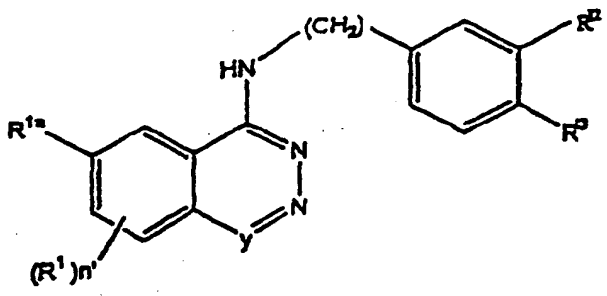
[0011] As defined above, R^7 and R^8 together with the nitrogen atom to which they are bonded may form a ring which may be substituted, and examples of the ring include piperidinyl, pyrrolidinyl and piperazinyl.
The substituent for the ring includes a hydroxyl group, an optionally substituted amino group, an aminoalkyl group, a nitro group, a nitroalkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a hydroxyalkyl group, an optionally protected carboxyl group and an optionally protected carboxyalkyl group, among which a hydroxyl group, a hydroxymethyl group, a hydroxyethyl group, a carboxymethyl group and a carboxyethyl group are preferable.

[0012] The halogen atom as defined with respect to B, R^1, R^{1a}, R^{12}, R^{13} and R^{14} includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

[0013] The pharmacologically acceptable salt according to the present invention includes inorganic acid salts such as hydrochloride, sulfate, hydrobromide and phosphate; and organic acid salts such as formate, acetate, trifluoroacetate, maleate, fumarate, tartrate, methanesulfonate, benzenesulfonate and toluenesulfonate.

[0014] Although several compounds according to the present invention form hydrates, it is needless to say that the hydrates fall within the scope of the present invention.

[0015] Among the compounds of the present invention, fused pyridazine compounds represented by the following general formula (II) and pharmacologically acceptable salts thereof are preferable:

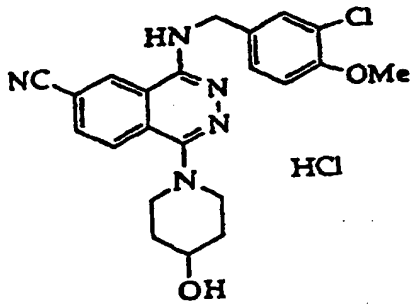


II

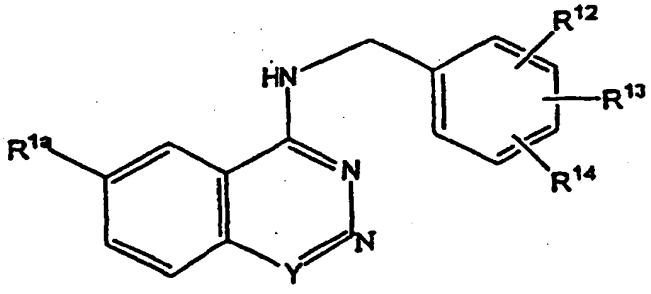
wherein

R^1, R^{1a}, R^{12} and R^{13} are each as defined above ;
y represents = C-B;
wherein B is as defined above ;and
n' is an integer of 1 to 3.

[0016] Even more preferable are fused pyridazine compounds represented by the general formula (II) and pharmacologically acceptable salts thereof wherein B is $-NR^7R^8$ and R^1 is hydrogen. Most preferable is a fused pyridazine compound or a physiologically acceptable salt thereof represented by the following formula:



[0017] Further, fused pyridazine compounds represented by the following general formula (V) and pharmacologically acceptable salts thereof are desirable:



V

(wherein R^{1a} represents a halogen atom, a nitro group, an amino group, a cyano group or a 4-hydroxypiperidin-1-yl group and y is defined as above.

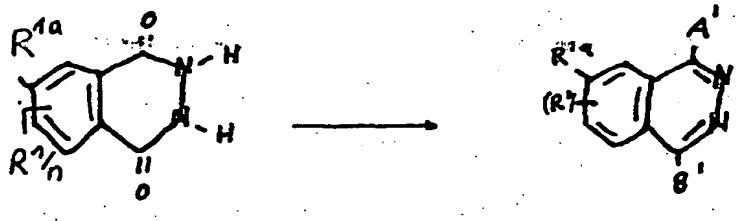
[0018] R^{12}, R^{13} and R^{14} represent each independently a hydrogen atom, a halogen atom, a methoxy or an ethoxy

group.

[0019] The compounds of the present invention can be readily prepared by known processes or combinations of known processes. Several main processes for the preparation of the compounds of the present invention will now be described, though it is needless to say that the compounds of the present invention are not limited to those prepared by these processes.

Preparation process 1

[0020] A compound represented by the general formula (VIII) can be prepared by the following process:



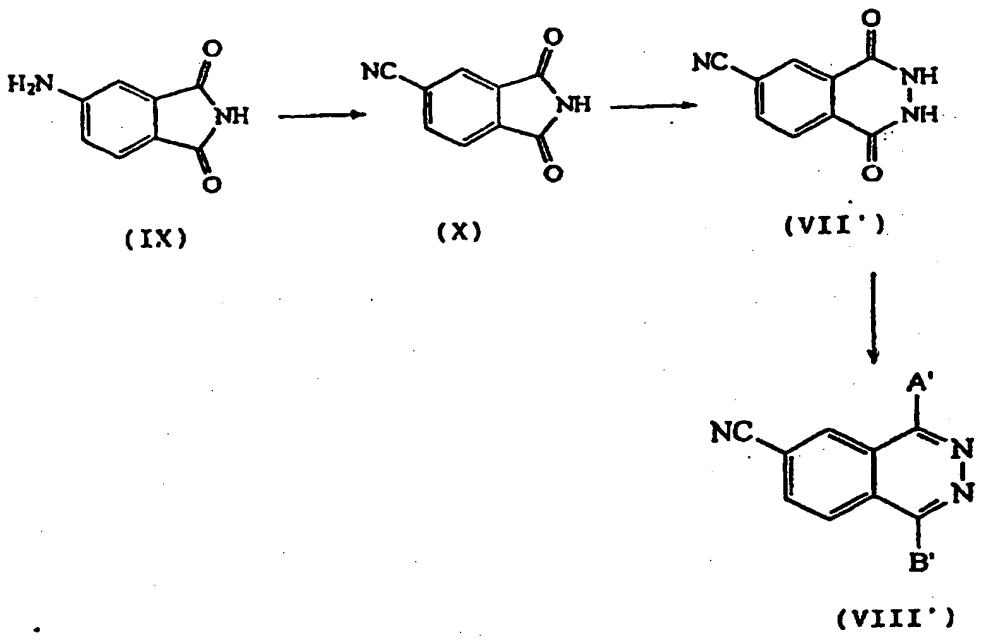
(VII) (VIII)

(wherein A' and B' represent each independently a halogen atom; and R^1, R^{1a} and n are each as defined above)

[0021] Specifically, the above compound can be prepared by halogenating a corresponding 1,4-phthalazinedione derivative. This halogenation can be conducted in a conventional manner. Examples of the chlorinating agent usable in this case include phosphorus pentachloride, phosphorus oxychloride and mixture of both. Although the halogenation can be conducted without any solvent, any solvent inert to the halogenation may be used. In some cases, the use of a tertiary amine such as diisopropylethylamine or N,N-dimethylformamide gives better results. The reaction temperature preferably ranges from about room temperature to about 150°C.

Preparation process 2

[0022] A compound represented by the general formula (VIII') wherein A' and B' represent each independently a halogen atom and R^{1a} represents a cyano group can be prepared also by the following process:



(1st step)

[0023] In this step, the amino group of 4-amino-phthalimide is converted into a cyano group. This conversion is preferably conducted by the Sandmeyer reaction, though it may be conducted by any conventional process. According to the Sandmeyer reaction, the conversion is conducted by converting 4-aminophthalimide into a diazonium salt in a conventional manner and thereafter reacting the diazonium salt with a nucleophilic reagent such as copper salt to replace the diazonium group by a cyano group. Although commercially available copper cyanide may be used in this reaction, better results can be attained by the use of the copper cyanide prepared from potassium cyanide and cuprous chloride just before use.

(2nd step)

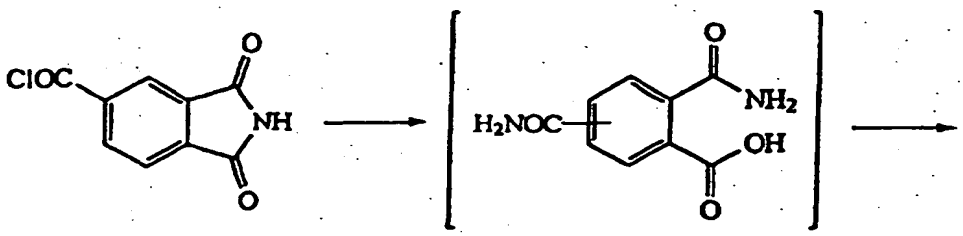
[0024] In this step, the phthalimide derivative prepared in the 1 st step is converted into a corresponding 1,4-phthalazinidione. This conversion can be conducted according to the process described in Castle: "HETEROCYCLIC COMPOUNDS", Vol.27.

(3rd step)

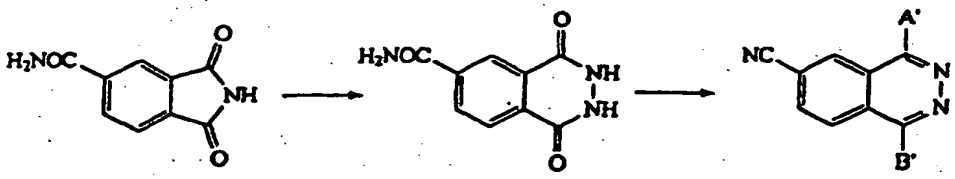
[0025] In this step, the 1,4-phthalazinedione prepared in the above 2nd step is prepared according to Preparation process 1.

Preparation process 3

[0026] A compound represented by the general formula (VIII') wherein R^{1a} represents a cyano group can be prepared also by the following process:



(XI) (XII)



(XIII) (XIV) (VIII')

(wherein A' and B' are each as defined above) (1st step)

[0027] In this step, 4-carbamoylphthalimide is prepared by reacting trimellitoyl chloride with ammonia and dehydrating the obtained product. Specifically, this reaction is conducted by reacting trimellitoyl chloride with aqueous ammonia either without any solvent or in a state dissolved in a solvent at a temperature ranging from about -15°C to room temperature. The solvent to be used in this case is preferably acetone. dichloromethane, chloroform or ethyl acetate, though any organic solvent inert to the reaction may be used. The resulting reaction mixture is treated with an acid to give a mixture comprising 2,4-dicarbamoylbenzoic acid and 2,5-dicarbamoylbenzoic acid. This mixture is further treated in the absence or presence of a solvent for 0.5 to 24 hours to give the objective compound. This treatment is conducted at room temperature to about 200°C. The solvent to be used in this treatment is preferably N-methyl-2-pyrrolidinone, though any solvent inert to the reaction may be used.

(2nd step)

[0028] In this step, the phthalimide derivative prepared in the above 1st step is converted into a phthalazinedione in a conventional manner.

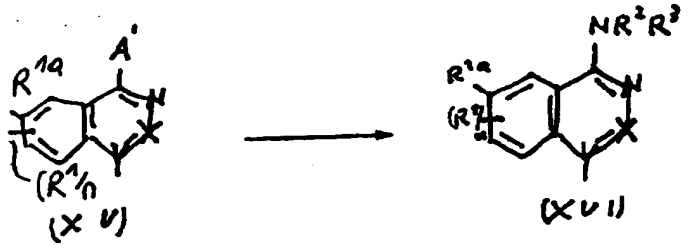
[0029] This conversion can be conducted by a conventional process such as reaction with hydrazine hydrate or the like. The reaction temperature is preferably 0°C to room temperature.

(3rd step)

[0030] In this step, the 6-carbamoyl-2,3-dihydro-1,4-phthalazinedione prepared in the 2nd step is converted into 6-cyano-1,4-dichlorophthalazine through dehydration and chlorination. The reagent useable in this case includes phosphorus oxychloride, thionyl chloride, phosphorus pentachloride and mixtures of two or more of them. The reaction temperature may range from room temperature to the boiling point of the reagent and the reaction time is about 0.5 to 36 hours. In some cases, better results can be attained by the addition of N,N-dimethylformamide or a tertiary amine such as diisopropylethylamine.

Preparation process 4

[0031] A compound represented by the formula (XVI) wherein R^2 and R^3 represent each independently a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted arylalkyl group or an optionally substituted heteroarylalkyl group, or alternatively R^2 and R^3 together with the nitrogen atom to which they are bonded may form a ring which may be substituted and B represents a halogen atom can be prepared by the following process:



(wherein A' represents a halogen atom; and R^1, R^2, R^3, X and Y are each as defined above).

[0032] Specifically, the above compound is prepared through the conventional substitution reaction. The solvent to be used in the reaction may be any organic one inert to the reaction, and preferable examples of the solvent include alcohols such as isopropyl alcolhol; ethers such as tetrahydrofuran and 1,4-dioxane; dimethylformamide, dymethylacetamide and N-methyl-2-pyrrolidinone.

[0033] The reaction temperature may preferably range from about room temperature to the refluxing temperature of the solvent.

[0034] Better results can be attained by the addition of a salt such as potassium carbonate, sodium carbonate or barium carbonate, or a tertiary amine such as diisopropylethylamine or DBU. In particular, the addition of a tertiary amine such as diispropylethylamine or DBU can give the best results.

[0035] After the completion of the reaction, the reaction mixture is post-treated in a conventional manner and is freed from undesirable isomers by recrystallization or treatment with a column to give an objective compound.

Preparation process 5

[0036] A compound represented by the general formula (XVIII) can be prepared also by the following process:

(XVII) (XVIII)

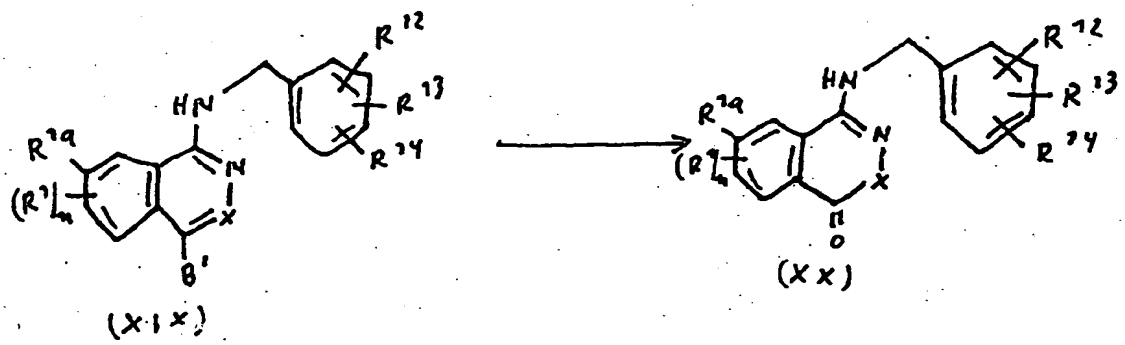
(wherein R^1, R^{1a}, R^{12}, R^{13}, R^{14}, B, A', B' , X and n are each as defined above)

[0037] According to this process, the objective compound is prepared from the halophthalazine derivative prepared by Preparation process 4 or the like through conventional replacement. The solvent to be used in this case is preferably N-methyl-2-pyrrolidinone, though any solvent inert to the reaction may be used. The reactant B-H is used in excess based on the starting halophthalazine derivative. In some cases, better results can be attained by the addition of an organic base such as diisopropylethylamine, a salt such as potassium carbonate, sodium carbonate or sodium hydrogencarbonate, or an acid such as p-toluenesulfonic acid. Further, still better results can be attained by using hydrochloride of the compound B-H without the above additive.

[0038] The reaction temperature may be from about room temperature to the boiling point of the solvent. preferably 100°C or above.

Preparation process 6

[0039] A compound represented by the general formula (XX) wherein Y is -CO- can be prepared by the following process:



(wherein R^1, R^{1a}, R^{12}, R^{13}, R^{14}, B', X and n are each as defined above).

[0040] According to this process, the objective compound is prepared by hydrolyzing a corresponding halophthalazine derivative in a conventional manner. Specifically, the compound can be prepared by heating the corresponding halophthalazine derivative in an acidic or alkaline solution. In some case, better results can be attained when the halophthalazine derivative is stirred under heating at 100 to 200°C in an organic solvent such as N-methyl-2-pyrrolidinone in the presence of acetic acid for about 0.5 to 12 hours.

[0041] Pharmacological Experimental Examples will now be described to illustrate the effects of the present invention.

Pharmacological Experimental Example

Experimental Example 1

Inhibitory activity against cGMP-PDE prepared from swine lung

1. Experimental method

[0042] The enzyme activity of the cGMP-PDE prepared from swine lung was determined according to the method of Thompson et al. This determination was conducted in the presence of 1mM EGTA by the use of 1mM cGMP as substrate. Each compound according to the present invention was dissolved in DMSO and thereafter added to the reaction system to determine the inhibitory activity of the compound. The final concentration of DMSO in the reaction solution was controlled to 5% or below.

[0043] The preparation of cGMP-PDE was conducted as follows.

[0044] Swine lung was minched, followed by the addition of five times (by volume) as much buffer A (comprising Tris/HCl (20 mM), Mg acetate (2 mM), 2-mercaptoethanol (10 mM), EGTA (0.1 mM) and PMSF (0.2 mM) and adjusted to pH7.4). The resulting mixture was homogenized and centrifuged at 1000 × g for 5 minutes. Ammonium sulfate was added to the obtained supernatant and the resulting mixture was centrifuged at 20000 × g for 45 minutes to collect a fraction precipitating between 30 and 40% saturation with ammonium sulfate. This fraction was dialyzed against buffer A and passed through a column of DEAE-Toyopearl 650S (a product of Tosoh, Tokyo, Japan). The column was washed with buffer A and subjected to gradient elution with 0.05 to 0.2 M NaCl/buffer A to collect a cGMP-PDE fraction.

[0045] This cGMP-PDE fraction was passed through Blue-Sepharose CL-6B (a product of Pharmacia, Uppsala, Sweden). The resulting column was washed with buffer A containing cAMP (10 mM) and NaCl (0.5 M) and eluted with buffer A containing cGMP (10 mM) and NaCl (0.5 M). The obtained fraction was dialyzed, concentrated and stored.

2. Experimental results

[0046] The cGMP-PDE inhibitory activities of the compounds of the present invention as determined by the above method are given in Table 1.

Ex. No.	cGMP-PDE inhibitory activity IC50(nM)	PAP lowering activity
1	1.7	≧3
3	0.18	-

(continued)

Ex. No.	cGMP-PDE inhibitory activity IC50(nM)	PAP lowering activity
5	0.015	10
6	1.2	1
7	0.03	10
8	0.70	10
9	0.01	10
10	0.11	-
16	≦0.01	-
18	0.53	3-10
19	0.12	0.3-1
24	1.41	3
25	4.0	1
29	3.74	1
30	4.4	1
33	1.9	≧1
34	1.8	≦0.33
40	0.37	1
41	2.1	≦0.33
44	1.88	1
45	0.052	-
46	0.10	10
50	12.6	≧1
47	0.23	10
49	4.59	≧1
53	20.4	1
60	0.32	0.33

Experimental Example 2

Pulmonary arterial pressure lowering activity on anesthetized thoracotomized dog by intravenous administration

1. Experimental method

[0047] Male and female hybrid dogs having a weight of about 10 kg were operated under enflurane anesthesia with N_2O/O_2 as carrier. Each dog was thoracotomized in the left fourth intercostal space and a pressure transducer (MPC-500 mfd. by Miller) was inserted into the pulmonary artery to determine the pulmonary arterial pressure (PAP). This experiment was conducted with the mean PAP (mPAP) increased by about 10 mmHg by lowering the pressure of oxygen fed by about 40% of the normal one. Each compound according to the present invention was dissolved in Polyethylene glycol 400 (a product of Wako Pure Chemical Industries, Ltd.) in a concentration of 1 mg/ml and, if necessary, further diluted with Polyethylene glycol 400. The resulting solution was intravenously administered to the dog through a polyethylene catheter indwelling in the femoral vein.

2. Experimental results

[0048] The PAP lowering activities of the compounds of the present invention as determined by the above method are given in Table 1 in terms of relative ratios to the activity of sodium 1-[chloro-4-(3,4-methylenedioxybenzyl)amino-quinazolin-2-yl]piperidine-4-carboxylate.

Experimental Example 3

In vitro platelet aggregation inhibiting activity

1. Experimental method

[0049] Blood specimens (100ml) were collected from the forearm vains of normal male volunteers (age: 30 to 40 years, weight: 60 to 75 kg) who had not taken any drug for at least one week therebefore. In order to prevent blood coagulation, a 3.8% sodium citrate solution (Citral, a product of Yamanouchi Pharmaceutical Co., Ltd.) was added to the blood in an amount of one tenth of the blood volume. The resulting blood was centrifuged at room temperature (22-25°C) at 700 rpm for 10 minutes to recover a supernatant as platelet rich plasma (PRP). A blood anticoagulant solution (a product of Terumo Corporation) was added to the PRP in a final concentration of 15 v/v%. The resulting mixture was centrifuged at room temperature at 3000 rpm for 10 minutes to give a platelet pellet. This platelet pellet was suspended in physiological saline solution containing 0.1% of EDTA and the resulting suspension was centrifuged again to give another platelet pellet. This pellet was suspended in Ca^{2+}-free Tyrode's solution in a final concentration of about 40×10^7/ml.

[0050] The platelet aggregation was determined according to the turbidimetric method of Born et al. with an aggregometer (PAM-8C mfd. by Mebanix). Each compound according to the present invention was dissolved in DMSO in a concentration of 50 mM, followed by serial dilution with Ca^{2+}-free Tyrode's solution. The Ca^{2+}-free Tyrode's solution was used also as control.

[0051] A mixture comprising 25 ml of each of the dilutions of the compound of the present invention prepared above and 200 ml of the washed platelet prepared above was incubated, followed by the addition of 25 ml of a platelet coagulant. The resulting mixture was observed for aggregation. The platelet coagulant used was 3 mg/ml collagen (a product of Hormon-Chemie), 0.3 mM U46619 (a product of Cayman Chemical) or 0.04 U/ml thrombin (a product of Sigma).

[0052] The inhibitory activities of the compounds of the present invention were represented in terms of inhibitory ratios based on the aggregation intensity of control (the area of turbidity chart of the aggregometer).

2. Experimental results

[0053] The platelet aggregation inhibiting activities of the compounds of the present invention as determined by the above method are given in Table 2 in terms of 50% aggregation inhibitory concentrations (mM).

	Coagulant		
Ex. No.	collagen	U46619	thrombin
3	11		5.6
17 (dihydrochloride-free)	20		21
30	28		
40 (hydrochloride)	61	63	80
50	55	37	61

[0054] It can be understood from the results of the above pharmacological experiments that the compounds of the present invention exhibit cGMP-PDE inhibitory activity, platelet aggregation inhibiting activity and pulmonary arterial pressure lowering activity. Accordingly, the compounds of the present invention are useful as preventive and therapeutic agents for diseases for which cGMP-PDE inhibiting action, platelet aggregation inhibiting action or pulmonary arterial pressure lowering action is efficacious. Specific examples of such diseases include ischemic heart diseases such as angina pectoris, myocardial infarct and chronic and acute heart failures; pulmonary hypertension accompanied by pulmonary heart and that not accompanied thereby; thrombosis caused by trauma of vascular wall, arterial sclerosis, vasculitis and so forth; hypertension caused by arterial sclerosis and others; brain circulatory disturbances such as

peripheral circulation failure and cerebral infarction; cerebral malfunction; and allergic diseases such as bronchial asthma, atopic dermatitis and allergic rhinitis.

[0055] The compounds of the present invention have higher water solubilities than those of the compounds of the prior art having similar activities and structures. Therefore, they are excellent in the migration into the living body in oral administration, which is an advantage of the compounds of the present invention.

[0056] Further, the compounds of the present invention are less toxic and highly safe, thus being extremely useful as drugs.

[0057] The compound of the present invention may be orally or parenterally administered as a therapeutic or preventive agent for the above diseases. Although the dose thereof is not particularly limited but varies depending upon the symptom, age, sex and drug sensitivity of patient; the method, timing and interval of administration; the properties and kind of preparation; the kind of active ingredient and so forth, the dose per adult a day is preferably about 0.1 to 1000 mg, which may be administered in one to several portions.

[0058] The compounds of the present invention can be converted into pharmaceutical preparations by the use of conventional carriers according to conventional processes.

[0059] More precisely, a solid preparation for oral administration according to the present invention is prepared by adding a filler and, if necessary, a binder, disintegrator, lubricant, color, corrigent and/or antioxidant to an active ingredient and shaping the obtained mixture into a tablet, coated tablet, granule, power or capsule.

[0060] Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide.

[0061] Examples of the binder include polyvinyl alcohol. polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin and pectin; and examples of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils.

[0062] Examples of the color include those authorized as pharmaceutical additives. Those of the corrigent include cocoa powder, menthol, aromatic powder, mentha oil, borneol and powdered cinnamon bark; and those of the antioxidant include those authorized as pharmaceutical additives such as ascorbic acid and α-tocopherol. Of course, the tablet and granule may be suitably coated with sugar, gelatin or the like, if necessary.

[0063] On the other hand, an injection according to the present invention is prepared by adding a pH modifier, buffer, suspending agent, solubilizing agent, stabilizer, tonicity agent, antioxidant and/or preservative to an active ingredient and formulating the mixture into an injection for intravenous, subcutaneous or intramuscular administration by a conventional process. If necessary, the injection may be freeze-dried.

[0064] Examples of the suspending agent include methylcellulose. Polysorbate 80, hydroxyethylcellulose, acacia, tragacanth powder, carboxymethylcellulose sodium and polyoxyethylene sorbitan monolaurate.

[0065] Further, examples of the solubilizing agent include polyoxyethylene hardened castor oil, Polysorbate 80, nicotinamide and polyoxyethylene sorbitan monolaurate.

[0066] Furthermore, examples of the stabilizer include sodium sulfite, sodium metasulfite and ether; and those of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

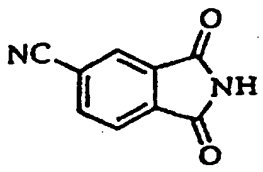
Example

[0067] Examples will now be described to facilitate the understanding of the present invention, though it is needless to say that the present invention is not limited to them. These Examples are preceded by Preparative Examples for starting compounds. For the sake of convenience, some compounds of the present invention are described as Preparative Examples, which does not limit the present invention.

Preparative Example 1

4-Cyanophthalimide

[0068]



[0069] 4-Aminophthalimide (40.0 g) was suspended in 300 ml of water, followed by the addition of 57 ml of concentrated hydrochloric acid. The obtained suspension was stirred under cooling with ice. A solution of 20.6 g of sodium nitrite in 69 ml of water was dropped into the above suspension at a bulk temperature of 5°C or below.

[0070] The obtained mixture was cooled to -20°C, followed by the addition of 300 ml of toluene. The resulting mixture was adjusted to pH7 with sodium hydrogencarbonate under vigorous stirring to form a diazonium salt.

[0071] Separately, a solution of 105.7 g of potassium cyanide in 206 ml of water was dropped into a suspension of 63.4 g of cuprous chloride in 250 ml of water, while the suspension was vigorously stirred under cooling with ice. The obtained mixture was further stirred under cooling with ice for one hour, followed by the addition of 500 ml of ethyl acetate. The diazonium salt prepared above was added into the resulting mixture in several portions and the obtained mixture was stirred under cooling with ice for one hour.

[0072] The resulting mixture was filtered through Celite to remove insolubles and the Celite was washed with an ethyl acetate/tetrahydrofuran mixture. The filtrates were together left standing to cause liquid-liquid separation. The organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate, dilute hydrochloric acid and a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and freed from the solvent by vacuum distillation. The title compound (41 g) was obtained as a reddish-brown solid.

M.p.: 237.0-238.0°C

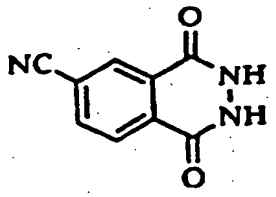
MASS: 173 (MH+)

1H-NMR (400 MHz, DMSO-d6) δ: 8.00(1H, dd, J=7.5, 1.0Hz), 8.29(1H, dd, J=7.5, 1.5Hz), 8.36(1H, dd, J=1.5, 1.0Hz), 11.73(1H, s)

Preparative Example 2

6-Cyano-2,3-dihydro-1,4-phthalazinedione

[0073]



[0074] 4-Cyanophthalimide (80 g) was suspended in 1000 ml of ethanol, followed by the addition of 25 ml of hydrazine monohydrate. The obtained mixture was stirred at room temperature for 5 hours.

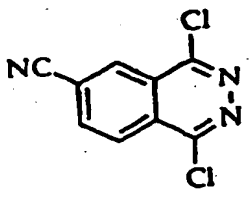
[0075] The resulting mixture was concentrated in a vacuum to about one-half its original volume, followed by the addition of 1000 ml of water. The obtained mixture was acidified with dilute hydrochloric acid to precipitate crystals, which were recovered by filtration to give 71 g of the title compound as a brown powder.

1H-NMR (400 MHz, DMSO-d6) δ: 8.19(1H, brs). 8.27(1H, dd, J=8.0, 1.0Hz), 8.48(1H, brs), 11.39(2H, brs)

Preparative Example 3

6-Cyano-1,4-dichlorophthalazine

[0076]



[0077] 6-Cyano-2,3-dihydro-1,4-phthalazinedione (69 g) was suspended in 400 ml of phosphorus oxychloride, followed by the addition of 75 ml of diisopropylethylamine. The obtained mixture was heated under reflux for 40 minutes.

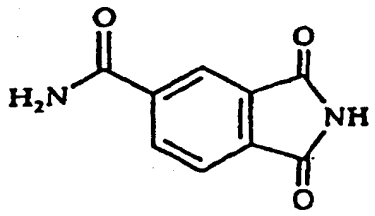
[0078] Excess phosphorus oxychloride was distilled away in a vacuum and the residue was dissolved in methylene chloride. The obtained solution was poured onto ice/water. The resulting mixture was filtered through Celite to remove insolubles and the Celite was washed weith methylene chloride. The filtrates were together extracted with methylene chloride and the organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate, dilute hydrochloric acid and a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and filtered through silica gel. The filtrate was distilled in a vacuum to remove the solvent. The title compound (66 g) was obtained as a palely yellowish-orange solid.

1H-NMR (400 MHz, CDCl3) δ: 8.24(1H, dd, J=8.5, 1.5Hz), 8.47(1H, dd, J=8.5, 1.0Hz), 8.68(1H, dd, J=1.5, 1.0Hz)

Preparative Example 4

4-Carbamoylphthalimide

[0079]



[0080] A solution of 21.1 g (0.10 mol) of trimellitoyl chloride in 25 ml of acetone was dropped into 200 ml of 29% aqueous ammonia, while the aqueous ammonia was stirred under cooling with ice. The resulting mixture was as such stirred for one hour, deaerated in a vacuum and acidified with concentrated hydrochloric acid under cooling with ice. The crystals thus precipitated were recovered by filtration, washed with water and dried with hot air to give 18.5 g of a mixture of 2,4-dicarbamoylbenzoic acid and 2,5-dicarbamoylbenzoic acid as a white crystal (yield: 89%).

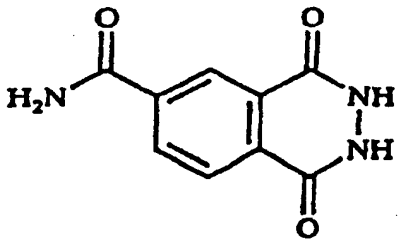
[0081] This mixture (16.0 g, 0.077 mol) was suspended in 80 ml of N-methyl-2-pyrrolidinone. The obtained suspension was stirred under heating at 150°C for 3 hours and cooled by allowing to stand, followed by the addition of 200 ml of water. The crystals thus precipitated were recovered by filtration, washed with water and dried with hot air. The title compound (13.3 g) was obtained as a light brown crystal (yield: 91%).

1H-NMR (400 MHz, DMSO-d6) δ: 7.70(1H, br s). 7.90(1H, dd, J=7.2, 1.2Hz), 8.28-8.31(2H, m), 8.32(1H, br s), 11.48 (1H, br s)

Preparative Example 5

6-Carbamoyl-2,3-dihydro-1,4-phthalazinedione

[0082]

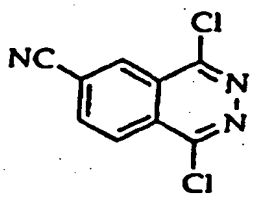


[0083] 4-Carbamoylphthalimide (2.00 g, 0.011 mol) was suspended in 12 ml of N-methyl-2-pyrrolidinone, followed by the dropwise addition of 0.8 ml of hydrazine hydrate. The obtained mixture was stirred at room temperature for 30 minutes, followed by the addition of 5.5 ml of 3N hydrochloric acid and 50 ml of water. The crystals thus precipitated were recovered by filtration, washed with water and dried with hot air. The title compound (2.0 g) was obtained as a light brown crystal (yield: 94%).
1H-NMR (400 MHz, DMSO-d6) δ : 7.68(1H, br s), 8.12(1H, br d, J=8.4Hz), 8.32(1H, dd, J=8.4, 1.6Hz), 8.39(1H, br s), 8.59(1H, br s), 11.69(2H, br s)

Preparative Example 6

6-Cyano-1,4-dichlorophthalazine

[0084]

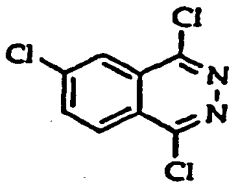


[0085] 6-Carbamoyl-2,3-dihydro-1,4-phthalazinedione (1.00 g, 0.0049 mol) was suspended in a mixture comprising 20 ml of phosphorus oxychloride and 20 ml of thionyl chloride. The obtained suspension was heated under reflux one whole day and night and distilled in a vacuum to remove the solvent. The obtained residue was dissolved in methylene chloride, followed by washing with water. The organic phase was dried over anhydrous magnesium sulfate and purified by silica gel column chromatography to give 0.76 g of the title compound as a light brown crystal (yield: 70%).

Preparative Example 7

1,4,6-Trichlorophthalazine

[0086]

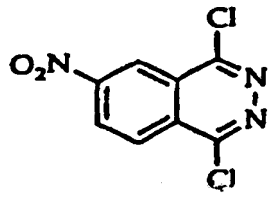


[0087] The title compound was prepared from 6-cyano-2,3-dihydro-1,4-phthalazinedione in a similar manner to that of Preparative Example 3.
1H-NMR (400 MHz, CDCl3) δ: 8.01(1H, dd, J=9.0, 2.0Hz), 8.29(1H, d, J=9.0Hz), 8.31(1H, d, J=2.0Hz)

Preparative Example 8

1,4-Dichloro-6-nitrophthalazine

[0088]

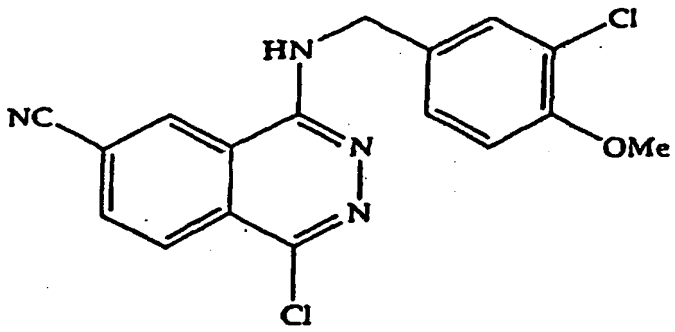


[0089] The title compound was prepared from 2,3-dihydro-6-nitro-1,4-phthalazinedione in a similar manner to that of Preparative Example 3.
1H-NMR (400 MHz. CDCl3) δ: 8.02(1H, dd, J=9.0, 0.5Hz), 8.83(1H, dd, J=9.0, 2.0Hz), 9.20(1H, dd. J=2.0, 0.5Hz)

Example 1

1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine

[0090]



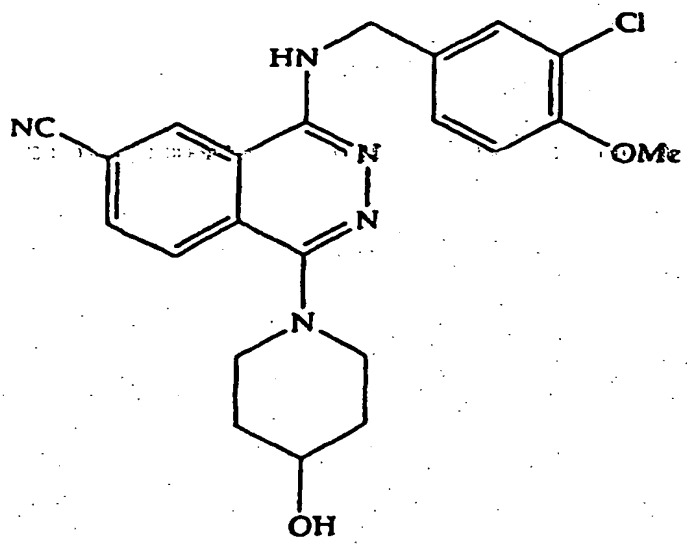
[0091] 6-Cyano-1,4-dichlorophthalazine (66. 2 g) prepared in Preparative Example 3 and 3-chloro-4-methoxybenzylamine (92 g) were suspended in 1200 ml of tetrahydrofuran, followed by the addition of 250 ml of triethylamine. The obtained mixture was heated under reflux for 6 hours.

[0092] The crystals thus precipitated were filtered out and the filtrate was concentrated in a vacuum. The residue was purified by silica gel column chromatography [solvent: toluene/tetrahydrofuran (10 : 1)] to recover a less polar product. The title compound (59 g) was obtained as a pale-yellow crystal.
M.p.: 213.0-214.5°C
MASS: 359 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 3.87(3H, s), 4.78(2H, d, J=5.0Hz), 5.75(1H, t. J=5.0Hz), 6.87(1H, d. J=8.5Hz), 7.31(1H, dd, J=8.5, 2.0Hz), 7.43(1H, d, J=2.0Hz), 8.05(1H, dd, J=8.5, 1.5Hz), 8.24(1H, dd, J=1.5, 1.0Hz), 8.29(1H, dd, J=8.5, 0.5Hz)

Example 2

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(4-hydroxypiperidino)phthalazine

[0093]



[0094] 1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine (10.0 g) prepared in Example 1 was dissolved in 50 ml of N-methyl-2-pyrrolidinone, followed by the addition of 43.32 g of 4-hydroxypyridine and 10 ml of diisopropylethylamine. The obtained mixture was heated at 170°C for 8 hours.

[0095] Ethyl acetate was added to the reaction mixture and the obtained mixture was washed with water three times and with a saturated aqueous solution of common salt once, dried over anhydrous magnesium sulfate and freed from the solvent by vacuum distillation. The residue was purified by silica gel column chromatography [solvent: methylene chloride/methanol (30 : 1)] to give 10. 1 g of the title compound as a yellow crystal.

M.p.: 172.0-173.5°C

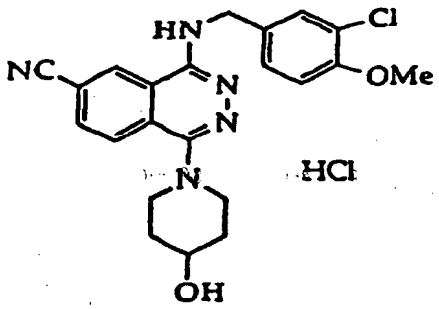
MASS: 424 (MH+)

1H-MNR (400 MHz, CDCl3) δ: 1.70(1H, brs), 1.80-1.90(2H, m), 2.07-2.15(2H, m), 3.05-3.15(2H, m). 3.50-3.60(2H, m), 3.87(3H, s), 3.90-4.00(1H, m), 4.74(2H, d, J=5.0Hz), 5.41(1H, t, J=5.0Hz), 6.87(1H, d, J=8.5Hz), 7.29(1H, dd, J=8.5, 2.0Hz), 7.42(1H, d, J=2.0Hz), 7.95(1H, dd, J=8.5, 1.5Hz), 8.12(1H, d, J=8.5Hz), 8.21(1H, s)

Example 3

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(4-hydroxypiperidino)phthalazine hydrochloride

[0096]



[0097] 1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine (10.0 g) prepared in Example 1 was dissolved in 50 ml of N-methyl-2-piperidone, followed by the addition of 43.32 g of 4-hydroxypiperidine and 10 ml of diisopropylethylamine. The obtained mixture was heated at 170° C for 8 hours.

[0098] Ethyl acetate was added to the reaction mixture. The obtained mixture was washed with water three times and with a saturated aqueous solution of common salt once, dried over anhydrous magnesium sulfate and freed from the solvent by vacuum distillation. The residue was purified by silica gel column chromatography [solvent: methylene chloride/methanol (30 : 1)] to give 10.1 g of 4-(3-chloro-4-methoxybenzyl)amino-6-cyano-1-(4-hydroxypiperidino) phthalazine as a yellow crystal. This product (10.8 g) was suspended in a mixture comprising 60 ml of ethanol and 30 ml of water, followed by the addition of 30 ml of 1N aqueous hydrochloric acid. The obtained mixture was dissolved by heating and cooled by allowing to stand at room temperature.

[0099] The crystals thus precipitated were recovered by filtration and dried with hot air at 80°C overnight to give 9.37 g of the title compound as a yellow crystal.

M.p.: 217-227 (dec.) °C

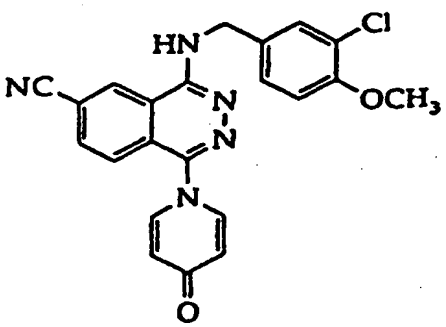
MASS: 424 (MH+)

1H-NMR (400 MHz, DMSO-d6) δ: 1.61-1.70(2H, m), 1.90-1.97(2H, m), 2.97-3.04(2H, m), 3.37-3.48(2H, m), 3.70-3.79 (1H, m), 3.84(3H, s), 4.70(2H, d. J=5.5Hz), 7.15(1H, d, J=8.5Hz), 7.44(1H, dd, J=8.5. 2.0Hz), 7.59(1H, d, J=2.0Hz), 8.23(1H, d. J=8.5Hz), 8.45(1H, d, J=8.5Hz). 9.33(1H, s), 10.10(1H, brs), 14.00(1H, brs)

Example 4

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-oxo-1,4-dihydropyrid-1-yl)phthalazine

[0100]

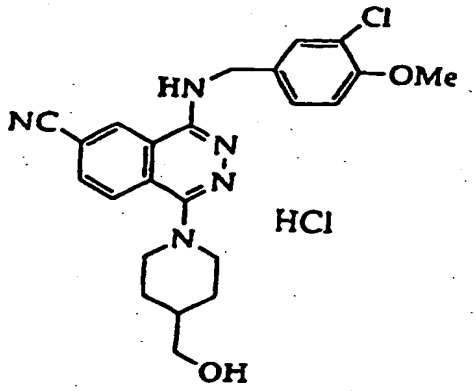


[0101] The title compound was prepared in a similar manner to that of Example 2.
M.p.: 218-219°C
MASS: 418 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 3.83(3H, s), 4.67(2H, d, J=5.6Hz), 7.11(1H, d, J=8.4Hz), 7.27(2H, dd, J=1.6Hz, 4.4Hz), 7.36(1H, dd, J=8.4, 2.0Hz), 7.48(1H, d, J=2.0Hz), 8.18-8.24(2H, m), 8.31(1H, dd, J=8.4, 1.2Hz), 8.56(2H, dd, J=1.6Hz, 4.4Hz), 9.02(1H, d, J=1.2Hz)

Example 5

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(hydroxymethyl)piperidino]phthalazine hydrochloride

[0102]

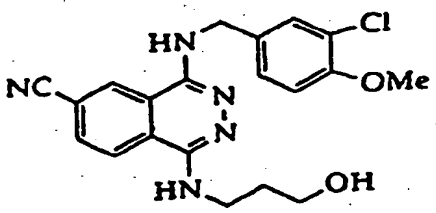


[0103] The title compound was prepared in a similar manner to that of Example 3.
MASS: 438 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.40-1.50(2H, m), 1.61(1H, bs), 1.78-1.84(2H, m), 2.82-2.91(2H, m), 3.33(2H, d, J=6.1Hz), 3.52-3.62(2H, m), 3.83(3H, s), 4.71(2H, d, J=5.0Hz), 7.14(1H, d, J=8.4Hz), 7.45(1H, dd, J=8.4Hz, 2.4Hz), 7.61(1H, d, J=2.4Hz), 8.21(1H, d, J=8.8Hz), 8.46(1H, d, J=8.8Hz), 9.42(1H, s)

Example 6

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(3-hydroxypropyl)aminophthalazine

[0104]

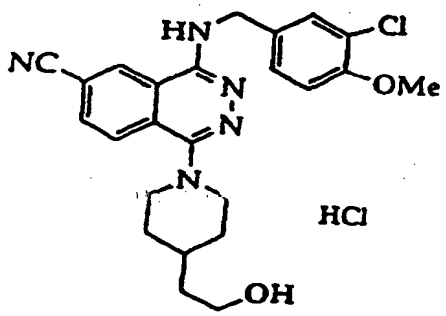


[0105] The title compound was prepared in a similar manner to that of Example 2.
M.p.: 132-135°C
MASS: 398 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.91-1.98(2H, m), 3.40(1H, br s), 3.71-3.76(1H, m), 3.80(2H, t, J=5.6Hz), 3.81(2H, t, J=5.6Hz), 3.91(3H, s), 4.68(2H, d, J=6.4Hz), 5.30-5.34(1H, t, J=6.4Hz), 6.92(1H, d, J=8.4Hz), 7.32(1H, dd, J=8.4, 2.4Hz), 7.46(1H, d, J=2.4Hz), 7.85(1H, d, J=8.8Hz), 7.95(1H, dd, J=8.8, 1.6Hz), 8.10(1H, d, J=1.6Hz)

Example 7

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(2-hydroxyethyl)piperidino]phthalazine hydrochloride

[0106]

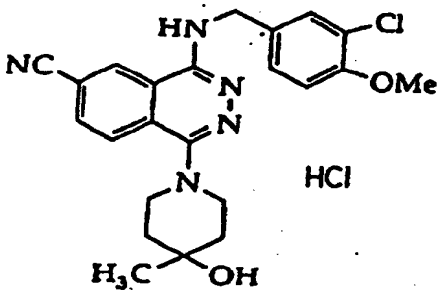


[0107] The title compound was prepared in a similar manner to that of Example 3
M.p.: 230 (dec.) ° C
MASS: 452 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.39-1.53(4H, m), 1.65(1H, m), 1.82(2H, m), 2.87(2H, m), 3.50(2H, t, J=6.8Hz), 3.56 (2H, m), 3.85(3H, s), 4.74(2H, d, J=5.3Hz), 7.15(1H, d, J=8.6Hz), 7.49(1H, dd. J=8.6, 2.0Hz), 7.63(1H, d, J=2.0Hz), 8.23(1H, d, J=8.6Hz), 8.47(1H, dd, J=8.6. 1.5Hz), 9.53(1H, br s)

Example 8

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(4-hydroxy-4-methylpiperidino)phthalazine hydrochloride

[0108]

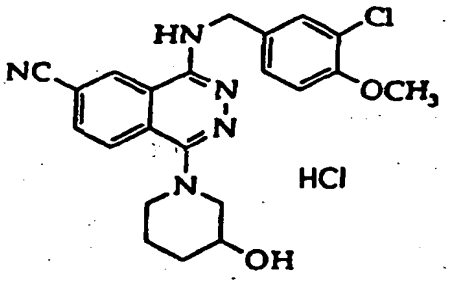


[0109] The title compound was prepared in a similar manner to that of Example 3.
M.p.: 230-240°C (dec.)
MASS: 438 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.22(3H, s), 1.61-1.71(2H. m), 1.73-1.84(2H, m), 3.18-3.33(4H, m), 3.85(3H, s), 4.76 (2H, d, J=5.1Hz), 7.15(1H, d, J=8.6Hz), 7.51(1H, dd, J=8.6, 2.0Hz), 7.66(1H, d, J=2.0Hz), 8.23(1H, d, J=8.4Hz), 8.46 (1H, dd, J=8.4, 1.0Hz), 9.63(1H, s)

Example 9

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(3-hydroxypiperidino)phthalazine hydrochloride

[0110]

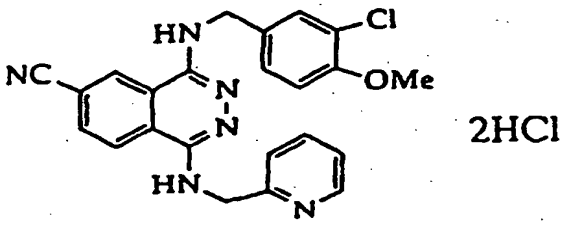


[0111] The title compound was prepared in a similar manner to that of Example 3.
M.p.: 189-199° C
MASS: 424 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.45(1H, m), 1.71 (1H, m), 1.84-1.97(2H, m), 2.86(1H, m), 2.98(1H, m), 3.32(1H, m), 3.42(1H, m), 3.83(1H, m) , 3.85(3H, s), 4.76(2H, d, J=5.7Hz), 7.16(1H, d, J=8.6Hz) , 7.51(1H, dd, J=8.6, 2.0Hz), 7.66(1H, d, J=2.0Hz) , 8.31(1H, d. J=8.4Hz), 8.49(1H, dd, J=8.4, 1.3Hz) , 9.61(1H, s)

Example 10

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(2-pyridylmethyl)aminophthalazine dihydrochloride

[0112]

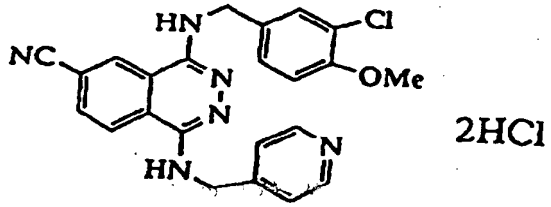


[0113] The title compound was prepared in a similar manner to that of Example 3.
M.p.: 188-190° C
MASS: 431 (MH+)
1H-NMR (400 MHz, CD3OD) δ: 3.83(3H, s), 4.62(2H, s), 5.05(2H, s), 7.08(1H, d, J=8.5Hz), 7.35(1H, dd, J=8.5, 2.0Hz), 7.47(1H, d, J=2.0Hz), 7.98(1H, ddd, J=8.0, 6.0, 1.5Hz), 8.16(1H, d, J=8.0Hz), 8.48(1H, dd, J=8.5, 1.5Hz), 8.57(1H, ddd, J=8.0, 8.0, 1.5Hz), 8.62(1H, d, J=8.5Hz). 8.76-8.78(1H, m), 9.06(1H, d. J=1.5Hz)

Example 11

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(4-pyridylmethyl)aminophthalazine dihydrochloride

[0114]

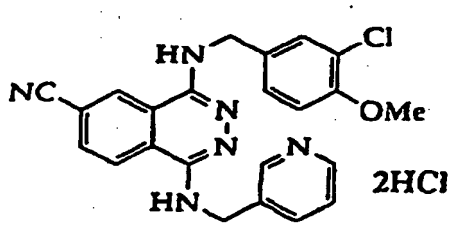


[0115] The title compound was prepared in a similar manner to that of Example 3.
M.p.: 212-214°C
MASS: 431 (MH+)
1H-NNR (400 MHz, CD3OD) δ: 3.88(3H, s) , 4.61(2H, s) , 4.97(2H, s), 7.08(1H, d, J=8.5Hz), 7.34(1H, dd, J=8.5, 2.0Hz), 7.47(1H, d, J=2.0Hz), 8.11-8.14(2H, m), 8.48(1H, dd, J=8.5, 1.5Hz), 8.61(1H, d, J=8.5Hz), 8.77-8.79(2H, m), 9.04(1H, d, J=1.5Hz)

Example 12

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(3-pyridylmethyl)aminophthalazine dihydrochloride

[0116]

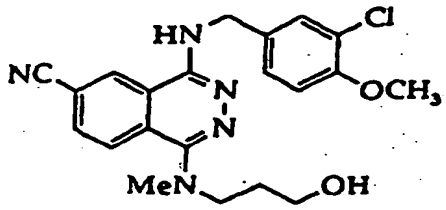


[0117] The title compound was prepared in a similar manner to that of Example 3
M.p. : 195,0-196,5° C
MASS: 431 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 3.84(3H, s), 4.59-4.63(2H, m), 4.78-4.82(2H, m), 7.12(1H, d, J=8.5Hz), 7.40(1H, dd, J=8.5, 2.0Hz), 7.55(1H, d, J=2.0Hz), 7.92(1H, dd, J=8.0, 5.5Hz). 8.46-8.52(1H, m), 8.58(1H, dd. J=8.5, 1.5Hz), 8.77 (1H, d, J=5.5Hz), 8.82-8.92(1H, m), 8.93 (1H, d, J=1.5Hz), 9.36-9.42(1H, m)

Example 13

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[N-(3-hydroxypropyl)-N-methylamino]phthalazine

[0118]

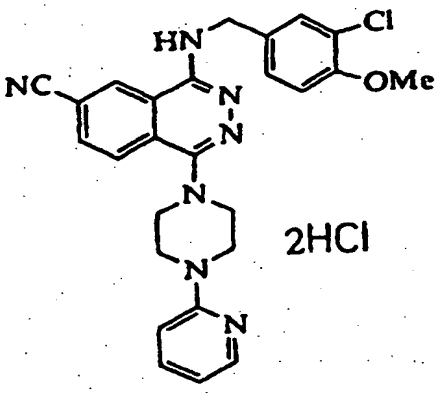


[0119] The title compound was prepared in a similar manner as that of Example 2.
M.p: amorphous
MASS: 412 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.72-1.79(1H, m), 2.83(3H, s) 3.14-3.22(2H, m), 3.41-3.48(2H, m), 3.83(3H, s), 4.45 (1H, t, J=4.8Hz), 4.64(2H, d, J=5.6Hz), 7.10(1H, d. J=8.0Hz), 7.36(1H, dd, J=8, 2Hz), 7.46(1H, d, J=2Hz), 7.85(1H, t, J=5.6Hz), 8.13-8.22(2H, m), 8.88(1H, d, J=1.2Hz)

Example 14

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(2-pyridyl)piperazin-1-yl]phthalazine dihydrochloride

[0120]

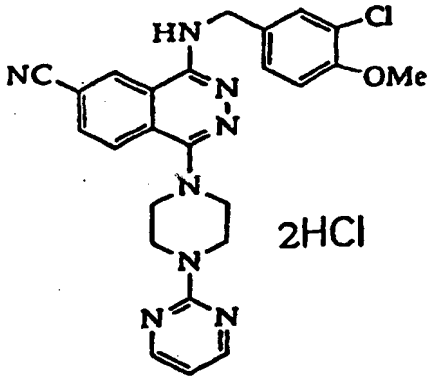


[0121] The title compound was prepared in a similar manner to that of Example 3.
M.p.: 205-215 (dec.) °C
MASS: 486 (MH+)
1H-NMR (400 MHz, CD3OD) δ: 3.59(4H, m), 3.90(3H, s), 4.01(4H, m), 4.74(2H, s), 4.07(1H, m), 7.12(1H, d, J=8.6Hz), 7.41(1H, dd, J=8.6, 2.4Hz), 7.50(1H, d. J=9.2Hz), 7.54(1H, d, J=2.4Hz), 8.02(1H, m), 8.11(1H, m), 8.44(1H, dd, J=8.4, 1.6Hz), 8.49(1H, dd, J=8.4, 0.8Hz), 9.09(1H, dd, J=1.6, 0.8Hz)

Example 15

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(2-pyrimidyl)piperazin-1-yl]phthalazine dihydrochloride

[0122]

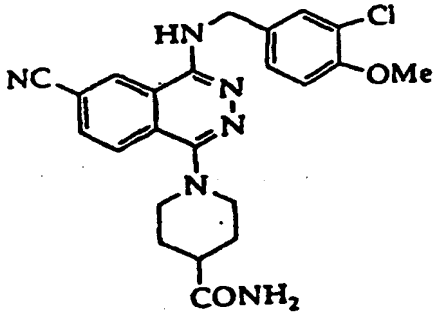


[0123] The title compound was prepared in a similar manner to that of Example 3
M.p.: 205-209 (dec.) °C
MASS: 487 (MH+)
1H-NMR (400 MHz, CD3OD) δ: 3.52(4H, m), 3.90(3H, s), 4.17(4H, m), 4.73(2H, s). 6.94(1H, t, J=4.8Hz), 7.12(1H, d, J=8.4Hz), 7.41(1H, dd, J=8.4, 2.4Hz), 7.54(1H, d, J=2.4Hz), 8.43(1H, dd, J=8.4, 1.6Hz), 8.49(1H, dd, J=8.4, 0.6Hz), 8.57(2H, d, J=4.8Hz), 9.08(1H, dd, J=1.6, 0.6Hz)

Example 16

1-(4-Carbamoylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine

[0124]

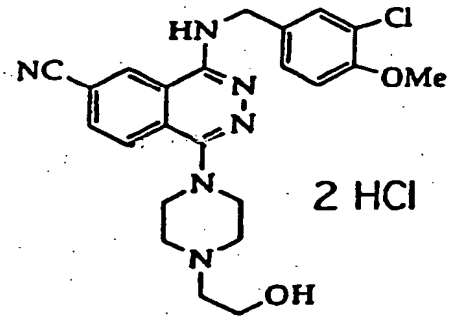


[0125] The title compound was prepared in a similar manner to that of Example 2.
M.p.: 228-230 (dec.)
MASS: 451 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ : 1.80-1.95(4H, m), 2.30(1H, m), 2.82(2H, m), 3.44(2H, m), 3.82(3H, s). 4.64(2H, d, J=5.8Hz), 6.80(1H, br s), 7.10(1H, d, J=8.4Hz), 7.32(1H, br s), 7.35(1H, dd, J=8.4, 2.0Hz), 7.46(1H, d, J=2.0Hz), 7.91 (1H, t, J=5.8Hz), 8.08(1H, d, J=8.8Hz), 8.20(1H, dd, J=8.8, 1.2Hz), 8.89(1H, d, J=1.2Hz)

Example 17

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(2-hydroxyethyl)piperazin-1-yl]phthalazine dihydrochloride

[0126]

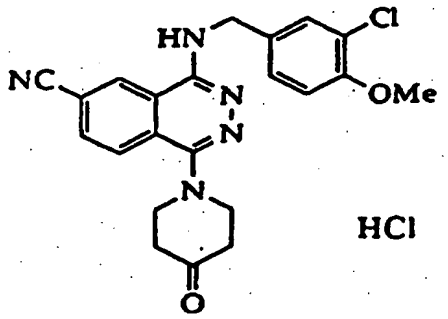


[0127] 4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-[4-(2-hydroxyethyl)piperazin-1-yl]phthalazine (12.0 g, 26.5 mmol) prepared in a similar manner to that of Example 2 was suspended in 600 ml of acetone, followed by the addition of 60 ml of 1N hydrochloric acid. The obtained mixture was stirred at room temperature for 30 minutes to precipitate crystals, which were recovered by filtration and dried at 90°C for 6 hours to give 13.06 g of the title compound as a pale-yellow powder.
M.p.: 185-189°C
MASS: 453 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 3.25-3.31(2H, m), 3.37-3.52(5H, m), 3.60-3.70(4H, m), 3.85(3H, s), 3.86(2H, br t, J=5.7Hz), 4.82(2H, d, J=5.7Hz), 7.16(1H, d, J=8.8Hz), 7.53(1H, dd, J=8.8. 2.0Hz), 7.67(1H, d, J=2.0Hz), 8.33(1H, d, J=8.4Hz), 8.65(1H, dd, J=8.4, 1.1Hz), 9.67(1H, s), 11.14(br, 1H)

Example 18

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1-(4-oxopiperidino)phthalazine hydrochloride

[0128]



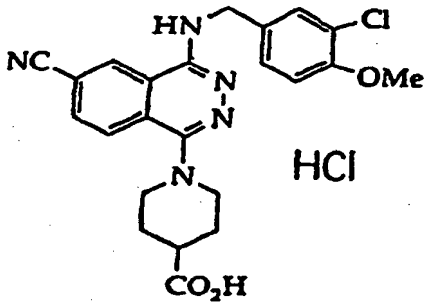
[0129] 4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1=(4,4-ethylenedioxypiperidino)phthalazine (565 mg, 1.21 mmmol) prepared in a similar manner to that of Example 2 was dissolved in 5 ml of trifluoroacetic acid. The obtained solution was stirred at room temperature for 18 hours and evaporated in a vacuum to dryness. The residue was dissolved in dichloromethane. The obtained solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with dichloromethane twice. The organic phases were combined, washed with water and

a saturated aqueous solution of common salt, dried over magnesium sulfate and freed from the solvent by vacuum distillation. The crude product thus obtained was purified by silica gel column chromatography [ethyl acetate/hexane (3 : 1)] to give 565 mg of a pale-yellow solid. This solid was recrystallized from 50% aqueous ethanol to give 423 mg (1.00 mmol) of 4-(3-chloro-4-methoxybenzyl)amino-6-cyano-1-(4-oxo-piperidino)phthalazine. This compound was convereted into a hydrochloride in the same manner as that employed in Example 3 for the formation of hydrochloride.
M.p.: 206°C (dec.)
MASS: 422 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ : 2.62-2.68(4H, m) , 3.55-3.61(4H, m), 3.85(3H, s). 4.77(2H, d, J=5.5Hz), 7.15(1H, d, J=8.5Hz). 7.49(1H, dd, J=8.5, 2.0Hz), 7.64(1H, d, J=2.0Hz), 8.40(1H, d, J=8.5Hz), 8.50(1H, dd, J=8.5, 1.5Hz), 9.55 (1H, d. J=1.5Hz)

Example 19

1-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine hydrochloride

[0130]



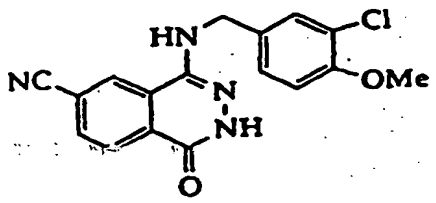
[0131] 1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine (2 g) prepared in Example 1 and t-butyl isonipecotate (2 g) were dissolved in 20 ml of N-methyl-2-pyrrolidone. The obtained solution was heated at 170°C for 5 hours and cooled, followed by the addition of water. The obtained mixture was extracted with ethyl acetate. The organic phase was washed with water, dried over anhydrous magnesium sulfate and concentrated in a vacuum. The obtained residue was subjected to silica gel column chromatography and eluted with toluene/tetrahydrofuran (10 : 1) to give 1.6 g of 1-(4-tert-butoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine.

[0132] 1-(4-tert-Butoxycarbonylpiperidino-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine (1.2 g) was stirred in 20 ml of formic acid at room temperature for 20 hours. The resulting mixture was concentrated in a vacuum and the obtained residue was subjected to silica gel column chromatography and eluted with dichloromethane/methanol (10 : : 1) to give 1.05_g of the title compound.
M.p.: >270°C
MASS: 452 (MH+)
1H-NMR (400 MHz. DMSO-d6) δ: 1.88-1.93(2H, m), 1.96-2.03(2H, m), 2.50-2.59(1H, m), 2.92-3.01(2H, m), 3.50-3.58 (2H, m), 3.85(3H, s), 4.74(2H, d, J=5.2Hz), 7.16(1H, d, J=8.4Hz), 7.48(1H, dd, J=8.4, 2.4Hz), 7.63(1H, d. J=2.4Hz), 8.26(1H, d. J=8.4Hz), 8.46(1H, dd, J=8.4, 1.2Hz), 9.49(1H, d, J=1.2Hz)

Example 20

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1(2H)-phthalazinone

[0133]



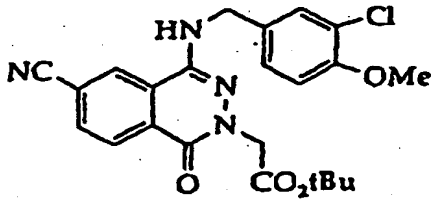
[0134] 1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-cyanophthalazine (1.0 g) prepared in Example 1 was dissolved in 10 ml of N-methyl-2-piperidone, followed by the addition of 0.26 ml of acetic acid and 2.1 ml of diisopropylethylamine. The obtained mixture was stirred at 170°C for 7 hours, followed by the addition of 100 ml of water. The crystals thus precipitated were recovered by filtration.

[0135] The crystals were recrystallized from ethanol/water to give 0.6 g of the title compound as a yellow crystal.
M.p.: 292.5-294°C
MASS: 341 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 3.81(3H, s), 4.36(2H, d, J=5.5Hz), 7.07(1H, d. J=8.5Hz), 7.29(1H, dd, J=8.5. 2.0Hz), 7.30(1H, t, J=5.5Hz), 7.41(1H, d, J=2.0Hz), 8.19(1H, dd, J=8.0, 1.0Hz), 8.32(1H, d, J=8.0Hz), 8.73(1H, d, J=1.0Hz), 11.86(1H, s)

Example 21

2-tert-Butoxycarbonylmethyl-4-(3-chloro-4-methoxybenzyl)amino-6-cyano-1(2H)-phthalazinone

[0136]

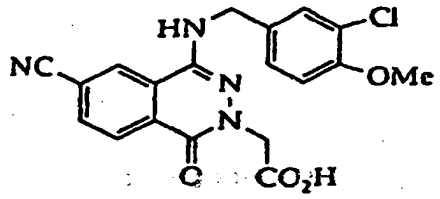


[0137] 4-(3-Chloro-4-methoxybenzyl)amino-6-cyanol-1(2H)-phthalazinone (0.20 g) prepared in Example 20 was dissolved in 5 ml of N-methyl-2-pyrrolidinone, followed by the addition of 0.14 g of t-butyl bromoacetate and 0.24 g of potassium carbonate. The obtained mixture was stirred at 80°C for 4 hours and poured into water, followed by extraction with ethyl acetate. The organic phase was washed with water twice and with a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and freed from the solvent by vacuum distillation. The title compound (0.41 g) was obtained as a yellow crystal.
M.p.: 173.5-175°C
MASS: 454 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.49(9H, s), 3.90(3H, s), 4.37(2H, d. J=5.0Hz), 4.91(2H, d, J=5.0Hz), 6.90(1H, d, J=8.5Hz), 7.25(1H, dd, J=8.5, 2.0Hz), 7.42(1H, d, J=2.0Hz), 7.93(1H, dd, J=8.0, 1.5Hz), 8.00(1H, d, J=1.5Hz), 8.53 (1H, d, J=8.0Hz)

Example 22

2-Carboxymethyl-4-(3-chloro-4-methoxybenzyl)amino-6-cyano-1(2H)-phthalazinone

[0138]

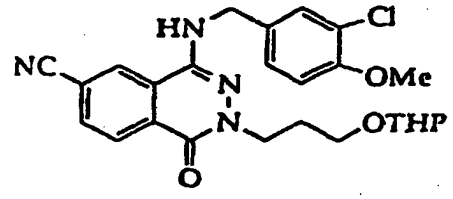


[0139] Trifluoroacetic acid (5 ml) was added to 0.41 g of the t-butyl ester prepared in Example 21. The obtained mixture was stirred at room temperature for one hour and freed from the trifluoroacetic acid by vacuum distillation. The obtained residue was recrystallized from ethanol/water to give 0.06 g of the title compound as a yellow crystal.
M.p.: 173-175°C
MASS: 399 (MH+)
1H-NMR (400 MHz. DMSO-d6) δ: 3.81(3H, s), 4.34(2H, d. J=5.5Hz), 4.62(2H, s), 7.06(1H, d, J=8.5Hz), 7.32(1H, dd, J=8.5, 2.0Hz), 7.43(1H, t, J=5.5Hz), 7.45(1H, d, J=2.0Hz), 8.22(1H, dd, J=8.0Hz, 1.0Hz), 8.34(1H, d, J=8.0Hz), 8.74 (1H, d, J=1.0Hz), 12.95(1H, br s)

Example 23

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-2-[3-(tetrahydropyran-2-yloxy)propyl]-1(2H)-phthalazinone

[0140]

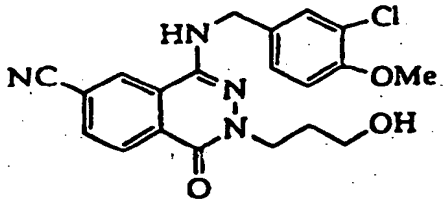


[0141] 4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-1(2H)-phthalazinone (0.20 g) prepared in Example 20 was dissolved in 5 ml of N-methyl-2-pyrrolidinone, followed by the addition of 0.24 g of 3-bromopropyl 2-tetrahydropyranyl ether and 0.24 g of potassium carbonate. The obtained mixture was stirred at 50°C for 4 hours and poured into water, followed by extraction with ethyl acetate. The organic phase was washed with water twice and with a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and freed from the solvent by vacuum distillation. The residue was purified by silica gel column chromatography [solvent: n-hexane/ethyl acetate (1 : 1)] to give 0.20 g of the title compound as a yellow crystal.
1H-NMR (400 MHz, CDCl3) δ : 1.44-1.83(6H, m). 2.08-2.17(2H, m), 3.45-3.51(2H. m), 3.81-3.87(2H, m), 3.89(3H, s), 4.17-4.30(2H, m), 4.46(2H, d, J=5.5Hz), 4.57-4.59(1H, m), 5.02(1H, t, J=5.5Hz), 6.90(1H, d, J=8.5Hz), 7.28(1H, dd, J=8.5, 2.0Hz), 7.44(1H, d, J=2.0Hz), 7.93(1H, dd, J=8.0, 1.5Hz), 8.06(1H, dd, J=1.5, 1.0Hz), 8.55(1H, dd, J=8.0, 0.5Hz)

Example 24

4-(3-Chloro-4-methoxybenzyl)amino-6-cyano-2-(3-hydroxypropyl)-1(2H)-phthalazinone

[0142]



[0143] Methanol (20 ml) and 1N hydrochloric acid (2 ml) were added to the 4-(3-chloro-4-methoxybenzyl)amino-6-cyano-2-[3-(tetrahydropyran-2-yloxy)propyl]-1(2H)-phthalazinone (0.20 g) prepared in Example 23. The obtained mixture was stirred at room temperature for 3 hours.

[0144] The solvent was distilled away in a vacuum and the residue was recrystallized from ethanol/water to give 0.14 g of the title compound as a yellow crystal.

M.p.: 191.5-193.0°C

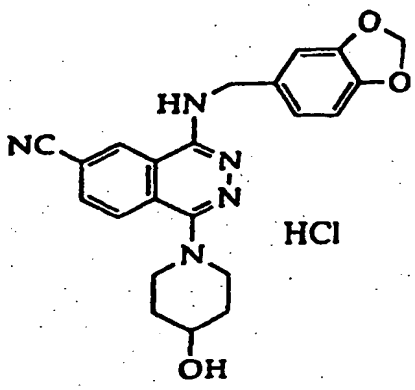
MASS: 399 (MH+)

1H-NMR (400 MHz, DMSO-d6) δ: 1.79(2H, quint, J=6.0Hz), 3.40(2H, q, J=6.0Hz), 3.81(3H, s), 3.99(2H, t, J=6.0Hz), 4.36(2H, d, J=5.5Hz), 7.07(1H, d, J=8.5Hz), 7.33(1H, dd, J=8.5, 2.0Hz), 7.45(1H, t, J=5.0Hz), 7.46(1H, d, J=2.0Hz) , 8.19(1H, dd, J=8.0, 1.5Hz), 8.34(1H, d, J=8.0Hz) , 8.71(1H, d, J=1.5Hz)

Example 25

6-Cyano-1-(4-hydroxypiperidino)-4-(3,4-methylenedioxybenzyl)aminophthalazine hydrochloride

[0145]



[0146] The title compound was prepared from 1-chloro-6-cyano-4-(3,4-methylenedioxybenzyl)aminophthalazine prepared in a similar manner to that of Example 1 in a similar manner to that of Example 3.

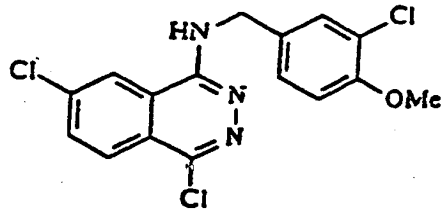
MASS: 404 (MH+)

1H-NMR (400 MHz, DMSO-d6) δ: 1.52-1.70(2H, m), 1.86-1.95(2H, m), 2.94-3.02(2H, m), 3.38-3.46(2H, m). 3.69-3.75 (1H, m), 4.73(2H, d, J=5.0Hz), 6.87(1H, d, J=8.0Hz), 7.04(1H, dd, J=8, 1.6Hz), 7.16(1H, d, J=1.6Hz), 8.19(1H, d, J=8.4Hz), 8.44(1H, d, J=8.4Hz), 9.69(1H, s)

Example 26

4-(3-Chloro-4-methoxybenzyl)amino-1,7-dichlorophthalazine

[0147]

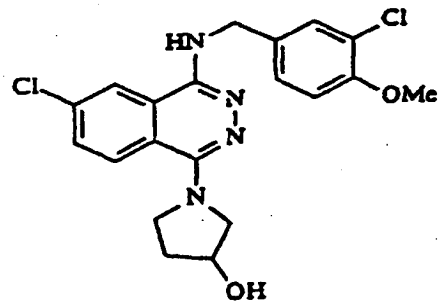


[0148] The title compound was prepared from 1.4.6-trichlorophthalazine prepared in Preparative Example 7 in a similar manner to that of Example 1.
M.p.: 197-198.5°C
MASS: 368 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 3.89 (3H, s), 4.78 (2H, d, J=5.5Hz), 5.32(1H, t, J=5.5Hz), 6.89(1H, d, J=8.5Hz), 7.32 (1H, dd, J=8.5, 2.0Hz), 7.45(1H, d, J=2.0Hz), 7.77(1H, d, J=2.0Hz), 7.82(1H, dd, J=9.0, 2.0Hz). 8.15(1H, d. J=9,0Hz)

Example 27

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(3-hydroxypyrrolidino)phthalazine

[0149]

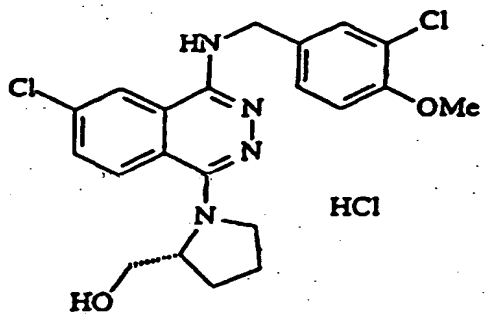


[0150] In a similar manner to that of Example 2, the title compound was prepared from 4-(3-chloro-4-methoxybenxyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 191-193°C
MASS: 419 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 2.01-2.08(1H, m), 2.14-2.24(1H, m), 3.56-3.64(1H, m), 3.73(1H, dt, J=14Hz, 4Hz), 3.82 (1H, dd, J=6Hz, 16Hz), 3.88(3H, s), 3.94(1H, dt, J=14Hz, 16Hz), 4.58-4.62(1H, m), 4.69(2H, d, J=6Hz), 4.83-4.90(1H, br t), 6.89(1H, d, J=8.4Hz), 7.31(1H, dd, J=2.2Hz, 8.4Hz), 7.45(1H, d, J=2.2Hz), 7.68(1H, dd, J=2.0Hz, 8.8Hz), 7.72 (1H, d, J=2.0Hz), 8.10(1H, d, J=8.8Hz)

Example 28

(R)-6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-[2-(hydroxymethyl)pyrrolidino]phthalazine hydrochloride

[0151]

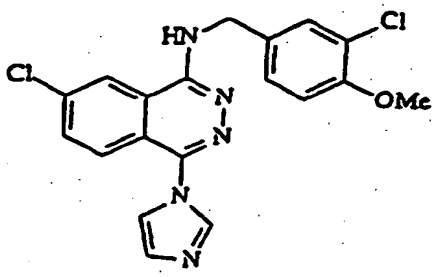


[0152] In a similar manner to that of Example 3, the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 163-165°C
MASS: 433 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.80-1.95(1H, m), 1.95-2.04(1H, m), 2.15-2.24(1H, m), 3.42-3.48(1H, m), 3.75(1H, dd, J=16Hz, 8Hz), 3.86(1H, dd, J=6Hz, 16Hz), 3.90(3H, s), 3.90-3.97(1H, m), 4.70(2H, d, J=6Hz), 4.70-4.77(1H, m), 4.83 (1H, br, t, J=6Hz), 6.91(1H, d, J=8.4Hz), 7.31(1H, dd, J=8.4, 2.2Hz), 7.45(1H, d, J=2.2Hz), 7.69(1H, dd, J=8.4Hz, 2.0Hz), 7.72(1H, d, J=2.0Hz), 8.08(1H, d, J=2.0Hz)

Example 29

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(imidazol-1-yl)phthalazine

[0153]

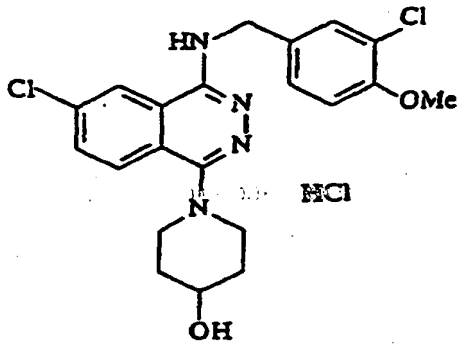


[0154] In a similar manner to that of Example 2, the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 221-222.5°C
1H-NMR (400 MHz, CDCl3) δ: 3.91(3H, s), 4.86(2H, d, J=5.5Hz), 5.56(1H, t, J=5.5Hz), 6.93(1H, d, J=8.5Hz), 7.31(1H, br s), 7.36(1H, dd, J=8.5, 2.0Hz), 7.41-7.42(1H, m), 7.48(1H, d, J=2.0Hz), 7.67(1H, d, J=9.0Hz), 7.81(1H, dd, J=9.0, 2.0Hz), 7.99(1H, br s)

Example 30

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(4-hydroxypiperidino)phthalazine hydrochloride

[0155]

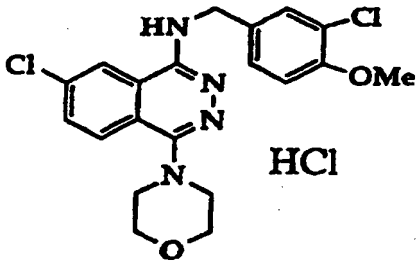


[0156] In a similar manner to that of Example 3 the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino- 1,6-dichlorophthalazine prepared in Example 26.
M.p.: 229-232 (dec.) °C
MASS: 433 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.60-1.70(2H, m), 1.86-1.96(2H, m), 2.95-3.06(2H, m), 3.38-3.48(2H, m), 3.69-3.78 (1H, m), 3.92(3H, s), 4.68(2H, d, J=4.6Hz), 7.13(1H, d, J=8.8Hz), 7.43(1H, d, J=8.8Hz), 7.58(1H, s), 8.06-8.15(2H, m), 9.01(1H, s)

Example 31

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-morpholinophthalazine hydrochloride

[0157]

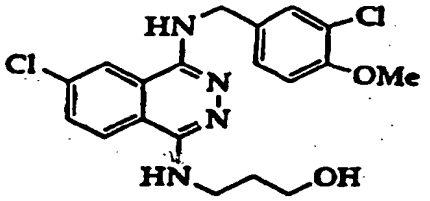


[0158] In a similar manner to that of Example 3 the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 255-261 (dec.) °C
MASS: 419 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 3.20-3.23(4H, m), 3.82-3.96(4H, m). 3.85(3H, s), 4.74(2H, d, J=6.0Hz), 7.15(1H, d, J=8.8Hz), 7.48(1H, dd, J=8.8, 2.0Hz), 7.63(1H, d, J=2.0Hz), 8.13(1H, dd, J=8.8, 2.0Hz), 8.21(1H, d, J=8.8Hz), 9.16 (1H, d, J=2.0Hz), 10.50(1H, br t), 13.97(1H, br s)

Example 32

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(3-hydroxypropyl)aminophthalazine

[0159]

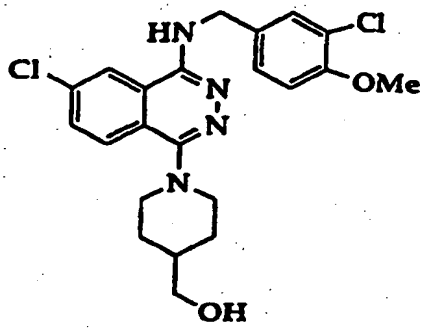


[0160] In a similar manner to that of Example 2, the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 131-138°C
MASS: 407 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.83-1.94(2H, m), 3.75(2H, t, J=5.4Hz), 3.80(2H, t, J=5.4Hz), 3.90(3H, s), 4.59(1H, br t, J=4.8Hz), 4.66(2H. d, J=4.8Hz), 5.14(1H, br t), 6.91(1H, d, J=8.4Hz), 7.32(1H, dd, J=8.4, 2.4Hz), 7.45(1H, d, J=2.4Hz), 7.69(2H, s), 7.72(1H, d, J=1.6Hz)

Example 33

6-Chloro-4-(3=chloro-4-methoxybenzyl)amino-1-[4-(hydroxymethyl)piperidino]phthalazine

[0161]

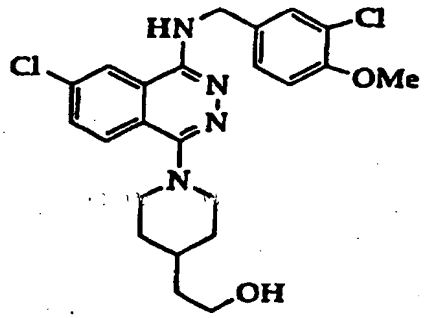


[0162] In a similar manner to that of Example 2, the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26
M.p.: 128-131°C
MASS: 447 (MH+)
1H-NMR (400 MHz, CDCl3) δ : 1.48-1.63(3H, m), 1.76(1H, m), 1.92(2H, m), 3.01(2H, dt, J=12.3, 2.0Hz), 3.59-3.67 (4H, m), 3.89(3H, s), 4.74(2H, d, J=5.1Hz), 4.99(1H, br t, J=5.1Hz), 6.89(1H, d, J=8.4Hz), 7.32(1H, dd, J=8.4, 2.2Hz), 7.45(1H, d, J=2.2Hz), 7.70(1H, dd, J=8.6, 1.8Hz), 7.73(1H, d, J=1.8Hz), 7.99(1H, d, J=8.6Hz)

Example 34

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-[4-(2-hydroxyethyl)piperidino]phthalazine

[0163]

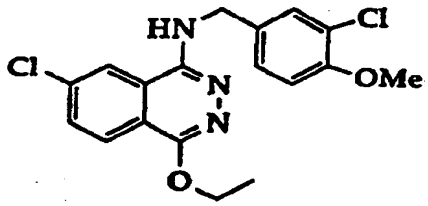


[0164] In a similar manner to that of Example 2, the title compound was prepared from 4-(3-chloro-4-methoxybenzyl) amino-1,6-dichlorophthalazine prepared in Example 26.
M.p.: 153-155°C
MASS: 461 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.41(br s), 1.54(2H, m), 1.60-1.76(3H, m), 1.88(2H, m), 2.98(2H, dt, J=12.5, 1.8Hz), 3.59(2H, m), 3.78(2H, br t, J=6.2Hz), 3.89(3H, s), 4.74(2H, d, J=5.3Hz), 5.00(1H, br t, J=5.3Hz), 6.89(1H, d, J=8.4Hz). 7.31(1H, dd, J=8.4, 2.2Hz). 7.45(1H, d, J=2.2Hz), 7.69(1H, dd, J=8.8, 2.0Hz), 7.73(1H, d, J=2.2Hz), 7.98(1H, d, J=8.8Hz)

Example 35

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-ethoxyphthalazine

[0165]

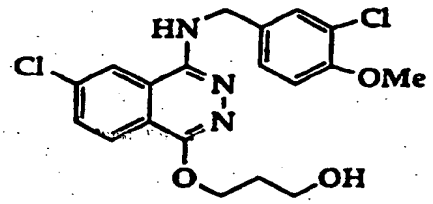


[0166] A solution of 120 mg of 60% oily sodium hydride in 20 ml of ethanol was added to 1.0 g of 4-(3-chloro-4-methoxybenzyl)amino-1,6-dichlorophthalazine prepared in Example 26. The obtained mixture was heated at 150° C in a sealed tube overnight, cooled and concentrated in a vacuum. The residue was dissolved in ethyl acetate. The obtained solution was washed with water and a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and concentrated in a vacuum. The obtained residue was subjected to silica gel column chromatography and eluted with dichloromethane/methanol (50 : 1) to give 0.9 g of the title compound.
M.p.: 111-115°C
MASS: 387 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.46(3H, t, J=7.2Hz), 3.82(3H, s), 4.43(2H, q, J=7.2Hz), 4.59(2H, d, J=5.6Hz), 7.08 (1H, d, J=8.4Hz), 7.33(1H, dd, J=8.4, 2.0Hz), 7.44(1H, d, J=2.0Hz), 7.65(1H, t, J=5.6Hz), 7.90(1H, dd, J=8.8, 2.0Hz), 8.03(1H, d, J=8.8Hz) , 8.45(1H, d, J=2.0Hz)

Example 36

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(3-hydroxypropyloxy)phthalazine

[0167]



[0168] 60% Sodium hydride (0.12 g, 3.0 mmol) was added to 8 ml of 1,3-propanediol. The obtained mixture was stirred at room temperature for one hour, followed by the addition of 1.0 g (2.7 mmol) of the compound prepared in Example 26. The obtained mixture was stirred at 150°C for one hour, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and freed from the solvent by distillation. The residue was purified by silica gel column chromatography [solvent: dichloromethane/methanol (30 : 1)] and recrystallized from aqueous ethanol to give 0.58 g of the title compound as white needles.

M.p.: 124-126°C

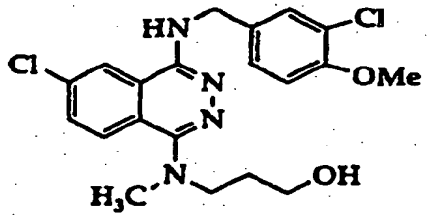
MASS: 408 (MH+)

1H-NMR (400 MHz, CDCl3) δ: 2.11(2H, quintet, J=6.0Hz), 3.22(1H, br s), 3.82(2H, br), 3.87(3H, s), 4.67(2H, d, J=5.3Hz), 4.70(2H, t, J=6.0Hz), 5.08(1H, t, J=5.3Hz), 6.85(1H, d, J=8.4Hz), 7.28(1H, dd, J=8.4, 2.2Hz), 7.42(1H, d, J=2.2Hz), 7.69(1H, dd, J=8.8, 1.8Hz), 7.75(1H, d, J=1.8Hz), 8.05(1H, d, J=8.8Hz)

Example 37

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-[N-(3-hydroxypropyl)-N-methylamino]phthalazine

[0169]



[0170] The compound (1.0 g, 2.7 mmol) prepared in Example 26 was dissolved in 9 ml of N-methyl-2-pyrrolidone, followed by the addition of 0.7 g (4.1 mmol) of N-methylpropanolamine hydrobromide and 1.14 g (8.2 mmol) of anhydrous potassium carbonate. The obtained mixture was stirred at 170°C for 7.5 hours, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous solution of common salt, dried over anhydrous magnesium sulfate and freed from the solvent by distillation. The residue was purified by silica gel column chromatography [solvent: dichloromethane/methanol (20 : 1)] and crystallized from dichloromethane/ether to give 37 mg of the title compound as white needles.

M.p.: 115-117° C

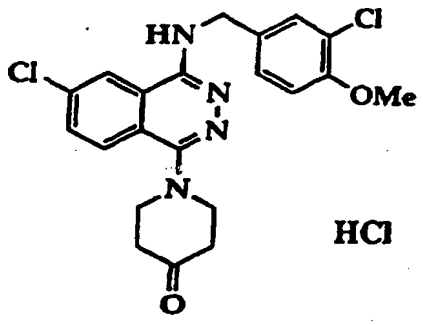
MASS: 421 (MH+)

1H-NMR (400 MHz, CDCl3) δ: 1.95(2H, quintet, J=6.0Hz), 2.85(1H, br s), 2.99(3H, s), 3.51(2H, t. J=6.0Hz), 3.75(2H, t, J=6.0Hz), 3.90(3H, s), 4.74(2H, d, J=5.3Hz), 4.95(1H, br), 6.91(1H, d, J=8.4Hz), 7.33(1H, dd, J=8.4. 2.0Hz), 7.46 (1H, d, J=2.2Hz), 7.72(1H, dd, J=9.3, 2.0Hz), 7.72(1H, d, J=2.0Hz), 8.05(1H, d, J=9.3Hz)

Example 38

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(4-oxopiperidino)phthalazine hydrochloride

[0171]

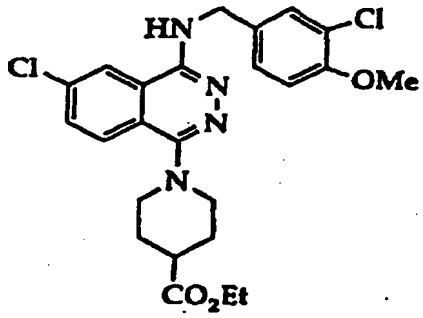


[0172] In a similar manner to that of Example 18, the title compound was prepared from the compound prepared in Example 26.
M.p.: 197 (dec.) °C
MASS: 431 (MH+)
1H-NNR (400 MHz, DMSO-d6) δ: 2.62-2.66(4H, m), 3.57-3.61(4H, m), 3.85(3H, s), 4.73(2H, d, J=6.0Hz), 7.16(1H, d, J=8.5Hz), 7.45(1H, dd, J=8.5, 2.0Hz), 7.60(1H, d, J=2.0Hz), 8.17(1H, dd, J=9.0, 2.0Hz), 8.28(1H, d, J=9.0Hz), 9.02 (1H, br s)

Example 39

6-Chloro-4-(3-chloro-4-methoxybenzyl)amino-1-(4-ethoxycarbonylpiperidino)phthalazine

[0173]

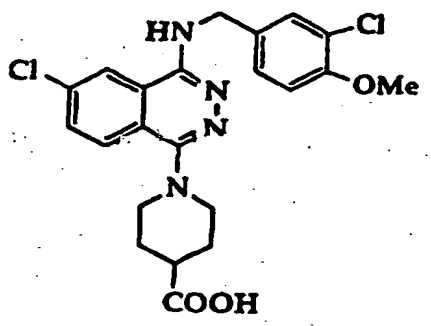


[0174] In a similar manner to that of Example 2, the title compound was prepared from the compound prepared in Example 26.
M.p.: 162-164.5°C
MASS: 489 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.29(3H, t, J=7.0Hz), 1.96-2.14(4H, m), 2.50-2.58(1H, m), 2.99-3.07(2H. m), 3.57-3.63 (2H, m), 3.91(3H, s), 4.19(2H, q, J=7.0Hz), 4.75(2H, d, J=5.0Hz), 4.92(1H, t, J=5.0Hz), 6.91(1H, d, J=8.5Hz), 7.32(1H, dd. J=8.5, 2.0Hz), 7.46(1H, d, J=2.0Hz), 7.70(1H, d, J=2.0Hz), 7.71(1H, dd, J=8.0, 2.0Hz), 7.99(1H, d, J=8.0Hz)

Example 40

1-(4-Carboxypiperidino)-6-chloro-4-(3-chloro-4-methoxybenzyl)aminophthalazine

[0175]

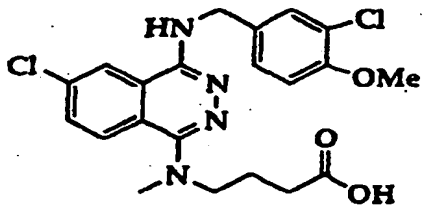


[0176] Methanol (50 ml), tetrahydrofuran (50 ml) and 1N aqueous solution (10 ml) of sodium hydroxide were added to 3.00 g of the compound prepared in Example 39. The obtained mixture was stirred at room temperature overnight and freed from the solvent by vacuum distillation. The residue was dissolved in 100 ml of water, followed by the addition of 10 ml of 1N hydrochloric acid. The crystals thus precipitated were recovered by filtration to give 2.76 g of the title compound as a pale-yellow crystal.
M.p.: 239.5-242°C (dec.)
MASS: 489 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.78-1.90(2H, m), 1.93-2.00(2H, m), 2.40-2.50(1H, m), 2.83-2.90(2H, m), 3.35-3.45 (2H, m), 3.82(3H, s), 4.61(2H, d, J=5.5Hz), 7.09(1H, d, J=8.5Hz), 7.33(1H, dd, J=8.5, 2.0Hz), 7.43(1H, d, J=2.0Hz), 7.75(1H, t, J=5.5Hz), 7.88(1H, dd, J=9.0, 2.0Hz), 7.98(1H, d, J=9.0Hz), 8.44(1H, d, J=2.0Hz)

Example 41

1-[N-(3-Carboxypropyl)-N-methylamino]-6-chloro-4-(3-chloro-4-methoxybenzyl)aminophthalazine

[0177]

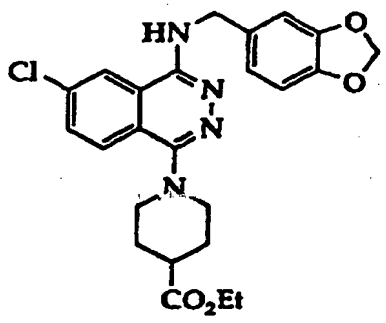


[0178] 6-Chloro-1-[N-(3-ethoxycarbonylpropyl)-N-methylamino]-4-(3-chloro-4-methoxybenzyl)aminophthalazine was prepared from the compound prepared in Example 26 in a similar manner to that of Example 2 and further converted into the title compound in a similar manner to that of Example 40.
M.p.: 248-250 (dec.) °C
1H-NMR (400 MHz, DMSO-d6) δ: 1.76-1.86(1H, m) , 2.06-2.14(1H, m) , 2.80(3H, s) , 3.06-3.14(2H, m) , 3.81 (3H, s), 4.59(2H, d, J=6Hz), 7.08 (1H, d, J=8.4Hz), 7.34(1H, dd, J=8.4, 2.2Hz), 7.44(1H, d, J=2.2Hz), 7.86-7.95(2H, m), 8.02 (1H, d, J=8.8Hz), 8.54(1H, d, J=2.0Hz)

Example 42

6-Chloro-1-(4-ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)aminophthalazine

[0179]

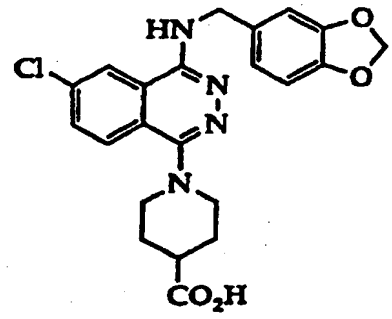


[0180] A mixture (4.83 g) comprising 1,6-dichloro-4-(3,4-methylenedioxybenzy)aminophthalazine and 4,6-dichloro-1-(3,4-methylenedioxybenzyl)aminophthalazine was prepared from 1,4,6-trichlorophthalazine (3.38 g) prepared in Preparative Example 7 and piperonylamine (2.21 g) in a similar manner to that of Example 1. The title compound (0.22 g) was prepared from 0.8 g of the mixture in a similar manner to that of Example 2 as a less polar product.
1H-NMR (400 MHz, CDCl3) δ: 1.28(3H, t, J=7.0Hz) , 1.90-2.10(4H, m), 2.46-2.55(1H, m), 2.96-3.05(2H , m), 3.53-3.60 (2H, m), 4.16(2H, q, J=7.0Hz) , 4.70(2H, d, J=5.0Hz), 5.21(1H, t, J=5.0Hz), 5.91(2H, s), 6.73(1H, d, J=8.0Hz), 6.87 (1H, dd, J=8.0, 1.5Hz), 6.91(1H, d, J=1.5Hz), 7.68(1H, dd, J=8.5, 2.0Hz), 7.78(1H, d, J=2.0Hz), 7.96(1H, d, J=8.5Hz)

Example 43

1-(4-Carboxypiperidino)-6-chloro-4-(3,4-methylenedioxybenzyl)aminophthalazine

[0181]

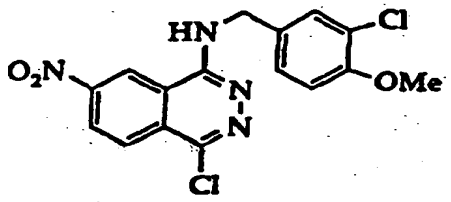


[0182] In a similar manner to that of Example 40 the title compound was prepared from the compound prepared in Example 42.
M.p.: 165-167° C
MASS: 441 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.80-1.91(2H, m), 1.94-2.01(2H, m), 2.43-2.52(1H, m), 2.86-2.94(2H, m), 3.40-3.50 (2H, m). 4.61(2H, d. J=5.0Hz), 5.98(2H, s). 6.87(1H, d, J=8.0Hz), 6.90(1H, dd, J=8.0, 1.0Hz), 7.00(1H, d. J=1.0Hz), 7.95(1H, br d, J=9.0Hz), 8.03(1H, d, J=9.0Hz), 9.58(1H, br s)

Example 44

1-Chloro-4-(3-chloro-4-methoxybenzyl)amino-6-nitrophthalazine

[0183]

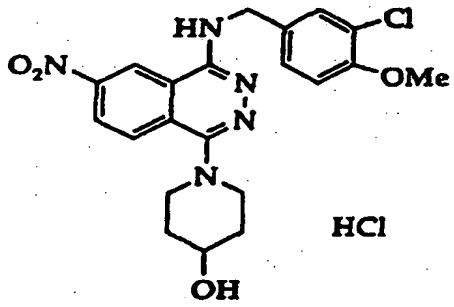


[0184] In a similar manner to that of Example 1, the title compound was prepared from 1,4-dichloro-6-nitrophthalazine prepared in Preparative Example 8.
M.p.: 217.0-217.5°C
MASS: 379 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 3.90(3H, s), 4.83 (2H, d, J=5.5Hz), 5.73(1H, t, J=5.5Hz), 6.91(1H, d, J=8.0Hz), 7.35 (1H, dd, J=8.0, 2.0Hz), 7.47(1H, d, J=2.0Hz), 8.38(1H, d, J=9.0Hz), 8.65(1H, dd, J=9.0, 2.0Hz), 8.73(1H, d, J=2.0Hz)

Example 45

4-(3-Chloro-4-methoxybenzyl)amino-1-(4-hydroxypiperidino)-6-nitrophthalazine hydrochloride

[0185]

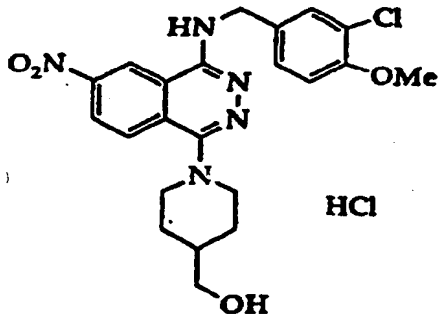


[0186] In a similar manner to that of Example 3, the title compound was prepared from the compound prepared in Example 44
M.p.: 245-246 (dec.) °C
MASS: 444 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.70(2H, m), 1.96(2H, m), 3.05(2H, m), 3.48(2H, m), 3.77(1H, m), 3.86(3H, s), 4.78 (2H, d, J=5.2Hz), 7.17(1H, d, J=8.4Hz), 7.48(1H, dd, J=8.4, 2.0Hz), 7.63(1H, d, J=2.0Hz), 8.34(1H, d, J=9.2Hz), 8.78 (1H, dd, J=9.2, 2.0Hz), 9.78(1H, d, J=2.0Hz), 10.59(1H, br s), 14.04(1H, br s)

Example 46

4-(3-Chloro-4-methoxybenzyl)amino-1-[4-(hydroxymethyl)piperidino]-6-nitrophthalazine hydrochloride

[0187]

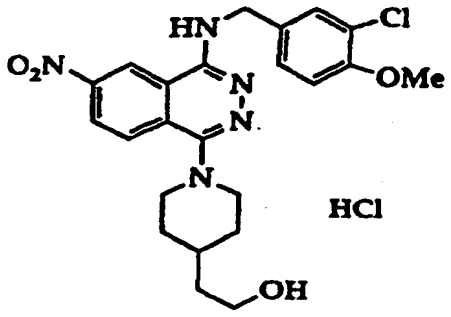


[0188] In a similar manner to that of Example 3, the title compound was prepared from the compound prepared in Example 44.
M.p.: 232-233 (dec.) °C
MASS: 458 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.48(2H m), 1.64(1H, m), 1.83(2H, m), 2.90(2H, m), 3.37(2H, d, J=6.4Hz), 3.61(2H, m), 3.85(3H, s), 4.77(2H, d, J=6.0Hz), 7.17(1H, d, J=8.4Hz), 7.48(1H, dd, J=8.4, 2.4Hz), 7.63(1H, d, J=2.4Hz), 8.32 (1H, d, J=9.2Hz), 8.78(1H, dd, J=9.2, 2.0Hz), 9.77(1H, d, J=2.0Hz), 10.56(1H, br s)

Example 47

4-(3-Chloro-4-methoxybenzyl)amino-1-[4-(2-hydroxyethyl)piperidino]-6-nitrophthalazine hydrochloride

[0189]

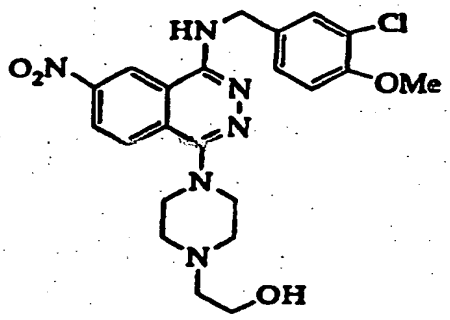


[0190] In a similar manner to that of Example 3, the title compound was prepared from the compound prepared in Example 44
M.p.: 233-236 (dec.) ° C
MASS: 472 (MH+)
1H-NMR (400 MHz. DMSO-d6) δ: 1.42-1.53(4H, m), 1.66(1H, m), 1.84(2H, m), 2.89(2H, m), 3.51 (2H, t, J=6.6Hz), 3.58(2H, m), 3.85(3H, s), 4.76(2H, d, J=5.6Hz), 7.17(1H, d, J=8.8Hz), 7.47(1H, dd, J=8.8, 2.0Hz), 7.62(1H, d, J=2.0Hz), 8.33(1H, d, J=8.8Hz), 8.77(1H, dd, J=8.8, 2.0Hz), 9.74(1H, d, J=2.0Hz), 10.45(1H, br s)

Example 48

4-(3-Chloro-4-methoxybenzyl)amino-1-[4-(2-hydroxyethyl)piperazin-1-yl]-6-nitrophthalazine

[0191]

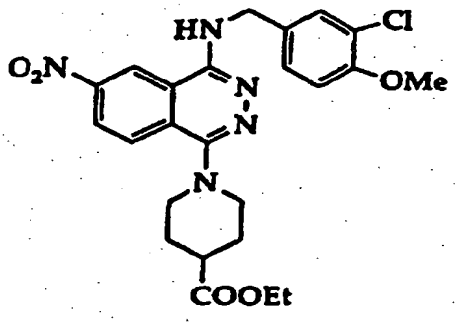


[0192] In a similar manner to that of Example 2, the title compound was prepared from the compound prepared in Example 44.
M.p.: 199-200 (dec.) °C
MASS: 473 (MH+)
1H-NMR (400 MHz, CDCl3) δ : 2.69(2H, t, J=5.4Hz), 2.80(4H, br s), 3.37(4H, br t), 3.70(2H, t, J=5.4Hz), 3.90(3H, s), 4.79(2H, d, J=5.2Hz), 6.87(1H, t, J=5.2Hz), 6.91(1H, d, J=8.4Hz), 7.37(1H, dd, J=8.4, 2.4Hz), 7.50(1H, d, J=2.4Hz), 8.16(1H, d, J=9.2Hz), 8.51(1H, dd, J=9.2, 2.0Hz), 9.13(1H, d, J=2.0Hz)

Example 49

1-(4-Ethoxycarbonylpiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-nitrophthalazine

[0193]

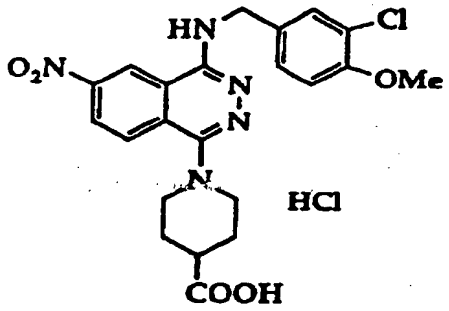


[0194] In a similar manner to that of Example 2, the title compound was prepared from the compound prepared in Example 44
M.p.: 208.5-209.5°C
MASS: 500 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.30(3H, t, J=7.0Hz), 2.01-2.15(4H, m), 2.53-2.59(1H, m), 3.04-3.11(2H, m), 3.56-3.64 (2H, m), 4.62(2H, s), 4.20(2H, q, J=7.0Hz), 4.79(2H, d, J=5.5Hz), 5.23(1H, t, J=5.5Hz), 6.84(1H, d, J=8.5Hz), 7.35(1H, dd, J=8.5, 2.0Hz), 7.48(1H, d, J=2.0Hz), 8.20(1H, d, J=2.0Hz), 8.55(1H, dd, J=9.0, 2.0Hz), 8.39(1H, d, J=2.0Hz)

Example 50

1-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-nitrophthalazine hydrochloride

[0195]

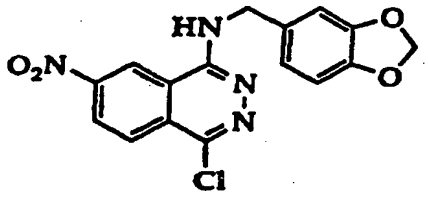


[0196] 1-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6-nitrophthalazine was prepared from the compound prepared in Example 49 in a similar manner to that of Example 40 and further converted into the title compound in the same manner as that employed in Example 3 for the formation of hydrochloride.
M.p.: 137-143 (dec.) °C
MASS: 472 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.85-1.92(2H, m), 1.97-2.05(2H, m), 2.50-2.60(1H, m), 2.96-3.03(2H, m), 3.52-3.56 (2H, m), 3.86(3H, s), 4.75(2H, d, J=4.5Hz), 7.18(1H, d, J=8.5Hz), 7.46(1H, m), 7.61(1H, d, J=2.0Hz), 8.36(1H, d, J=9.0Hz), 8.76(1H, dd, J=9.0, 2.0Hz), 9.70(1H, m)

Example 51

1-Chloro-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine

[0197]

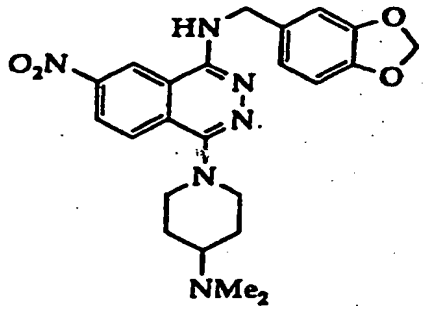


[0198] In a similar manner to that of Example 1, the title compound was prepared from 1,4-dichloro-6-nitrophthalazine prepared in Preparative Example 8.
M.p.: 186.5-188.0°C
MASS: 359 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 4.80(2H, d, J=5.0Hz), 5.73(1H, t, J=5.0Hz), 5.95(2H, s), 6.78(1H, d, J=8.0Hz), 6.92(1H, dd, J=8.0, 2.0Hz), 6.94(1H, d, J=2.0Hz), 8.37(1H, d, J=9.0Hz), 8.64(1H, dd, J=9.0, 2.0Hz), 8.73(1H, d, J=2.0Hz)

Example 52

1-(4-Dimethylaminopiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine

[0199]

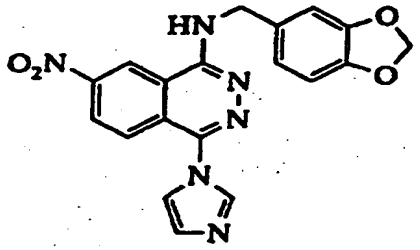


[0200] In a similar manner to that of Example 2, the title compound was prepared from 1-chloro-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine prepared in Example 51.
M.p.: 105.0-107.0 °C
MASS: 451 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.79(2H, ddd, J=13.0, 13.0, 4.0Hz), 2.04(2H, d, J=13.0Hz), 2.31-2.40(1H, m), 2.38(6H, s), 3.03(2H, dt, J=13.5, 1.5Hz), 3.66(2H, d, J=13.5Hz), 4.77(2H, d, J=5.0Hz), 5.15(1H, t, J=5.0Hz), 5.98(2H, s), 6.82 (1H, d, J=8.0Hz), 6.94(1H, dd, J=8.0, 1.5Hz), 6.97(1H, d, J=1.5Hz), 8.19(1H, d, J=9.0Hz), 8.54(1H, dd, J=9.0, 2.0Hz), 8.63(1H, d, J=2.0Hz)

Example 53

1-(Imidazol-1-yl)-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine

[0201]

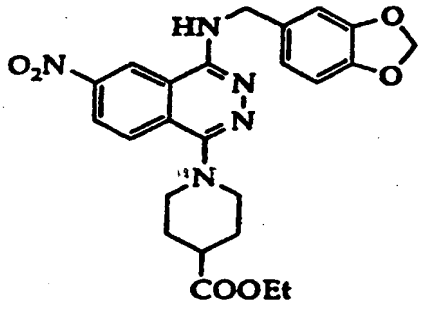


[0202] In a similar manner to that of Example 2, the title compound was prepared from 1-chloro-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine prepared in Example 51.
M.p.: 154.0-155.5°C
MASS: 391 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 4.89(2H, d, J=5.5Hz), 5.97(2H, s), 6.05(1H, t, J=5.5Hz), 6.82(1H, d, J=8.0Hz), 6.96(1H, dd, J=8.0, 2.0Hz), 6.98(1H, d, J=2.0Hz), 7.35(1H, s), 7.44(1H, s), 7.99(1H, d, J=9.0Hz), 8.02(1H, s), 8.61(1H, dd, J=9.0, 2.0Hz), 8.85(1H, d, J=2.0Hz)

Example 54

1-(4-Ethoxycarbonylpiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine

[0203]

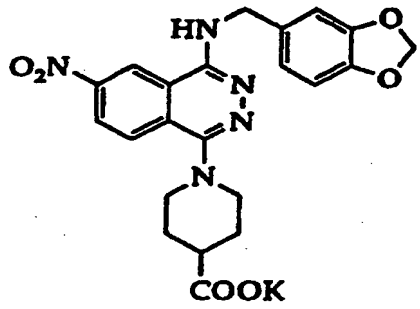


[0204] In a similar manner to that of Example 2, the title compound was prepared from the compound prepared in Example 51.
M.p.: 220-222° C
MASS: 480 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 1.30(3H, t, J=7.0Hz), 1.99-2.16(4H, m), 2.52-2.60(1H, m), 3.03-3.11(2H, m), 3.57-3.63 (2H, m), 4.20(2H, q, J=7.0Hz), 4.77(2H, d, J=5.0Hz), 5.17(1H, t, J=5.0Hz), 5.98(2H, s), 6.82(1H, d, J=8.0Hz), 6.94(1H, dd, J=8.0, 1.5Hz), 6.97(1H, d, J=1.5Hz), 8.20(1H, d, J=9.0Hz), 8.54(1H, dd, J=9.0, 2.0Hz). 8.64(1H, d, J=2.0Hz)

Example 55

Potassium salt of 1-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitrophthalazine

[0205]



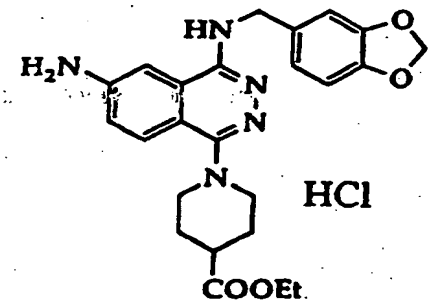
[0206] Potassium hydroxide (0.5 g) was dissolved in 30 ml of 50% aqueous methanol, followed by the addition of 0.26 g of the compound prepared in Example 54. The obtained mixture was stirred at room temperature for 4 hours.
[0207] The solvent was distilled away in a vacuum and water was added to the residue to form a solution. This solution was neutralized with dilute hydrochloric acid to precipitate a solid. This solid was recovered by filtration and dissolved in an aqueous solution of potassium carbonate. The obtained solution was adsorbed on an octadecylsilanol column and eluted with water/methanol to conduct purification. The obtained solid was crystallized from ethanol/ethyl acetate to give 0.15 g of the title compound as a pale-yellow solid.
M.p.: 206-209°C (dec.)
1H-NMR (400 MHz, DMSO-d6) δ: 1.64-1.76(2H, m), 1.76-1.84(2H, m), 1.84-1.92(1H, m), 2.65-2.73(2H, m), 3.26-3.32 (2H, m), 4.53(2H, d, J=5.5Hz), 5.90(1H, t, J=5.5Hz), 5.92(2H, s), 6.82(1H, d, J=8.0Hz), 6.85(1H, dd, J=8.0, 1.0Hz),

6.95(1H, d, J=1.0Hz), 7.04(1H, d. J=2.0Hz), 7.09(1H, dd, J=9.0, 2.0Hz), 7.64(1H, d, J=9.0Hz)

Example 56

6-Amino-1-(4-ethoxycarbonyzpiperidino)-4-(3,4-methylenedioxybenzyl)aminophthalazine hydrochloride

[0208]

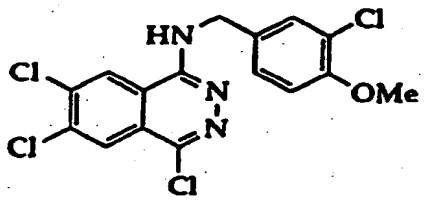


[0209] The compound (0.70 g) prepared in Example 54 was suspended in 50 ml of ethanol, followed by the addition of 50 ml of 10% palladium/carbon. The obtained mixture was stirred in a hydrogen atmosphere of 1 atm overnight and filtered to remove the catalyst. The filtrate was concentrated in a vacuum and the residue was dissolved in ethyl acetate. An excess of a 4N solution of hydrochloric acid in ethyl acetate was added to the obtained solution to form a hydrochloride. The solvent was distilled away in a vacuum. The obtained residue was recrystallized from ethanol/diisopropyl ether to give 0.54 g of the title compound as a white powder.
M.p.: 156.5-158.5°C
MASS: 450 (MH+)
1H-NMR (400 MHz, CD3OD) δ: 1.28(3H, t, J=7.0Hz), 1.95-2.03(2H, m), 2.04-2.12(2H, m), 2.57-2.65(1H, m), 2.99-3.11 (2H, m). 3.60-3.68(2H, m), 4.17(2H, q, J=7.0Hz), 4.62(2H, s), 5.94(2H, s), 6.80(1H, d, J=8.0Hz), 6.89(1H, dd, J=8.0, 2.0Hz), 6.92(1H, d, J=2.0Hz), 7.29(1H, br s), 7.31(1H, d, J=9.0Hz), 7.90(1H, d, J=9.0Hz)

Example 57

1-(3-Chloro-4-methoxybenzyl)amino-4,6,7-trichlorophthalazine

[0210]

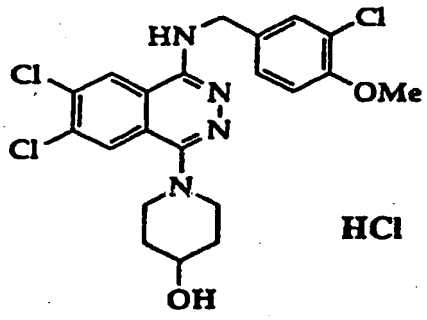


[0211] In a similar manner to that of Example 1, the title compound was prepared from 1.4,6,7-tetra-chlorophthalazine.
M.p.: 208-209°C
MASS: 404 (MH+)
1H-NMR (400 MHz, CDCl3) δ: 3.90(3H, s), 4.77(2H, d, J=5.0Hz), 5.29(1H, t, J=5.0Hz), 6.91(1H, d, J=8.0Hz), 7.32(1H, dd, J=8.0, 2.0Hz), 7.45(1H, d, J=2.0Hz), 7.89(1H, s), 8.28(1H, s)

Example 58

1-(3-Chloro-4-methoxybenzyl)amino-6,7-dichloro-4-(4-hydroxypiperidino)phthalazine hydrochloride

[0212]

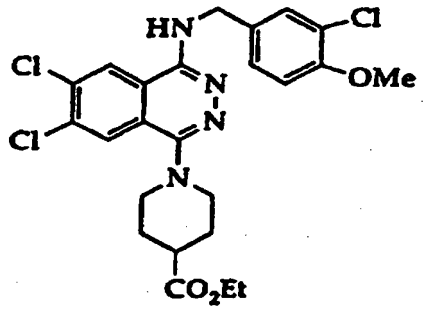


[0213] In a similar manner to that of Example 4, the title compound was prepared from the compound prepared in Example 57.
M.p.: 174.0-175.5°C
MASS: 467 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ : 1.63-1.73(2H, m), 1.91-1.99(2H, m), 3.00-3.08(2H, m), 3.39-3.49(2H, m), 3.73-3.81 (1H, m), 3.86(3H, s), 4.71(2H, d, J=6.0Hz), 7.14(1H, d, J=8.5Hz), 7.45(1H, dd, J=8.5, 2.0Hz), 7.59(1H, d, J=2.0Hz), 8.16(1H, s), 9.26(1H, s)

Example 59

1-(3-Chloro-4-methoxybenzyl)amino-6,7-dichloro-4-(4-ethoxycarbonylpiperidino)phthalazine

[0214]

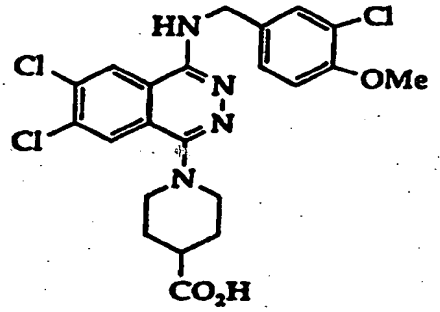


[0215] In a similar manner to that of Example 2, the title compound was prepared from the compound prepared in Example 57.
1H-NMR (400 MHz, CDCl3) δ: 1.29(3H, t, J=7.0Hz), 1.96-2.13(4H, m), 2.48-2.55(1H, m), 3.98-3.05(2H, m), 3.53-3.58 (2H, m), 3.86(3H, s), 4.19(2H, q, J=7.0Hz), 4.71(2H, d, J=5.0Hz), 5.31(1H, t, J=5.0Hz), 6.84(1H, d, J=8.5Hz), 7.27(1H, dd, J=8.5, 2.0Hz), 7.40(1H, d, J=2.0Hz), 7.94 (1H, s), 8.08(1H, s)

Example 60

1-(4-Carboxypiperidino)-4-(3-chloro-4-methoxybenzyl)amino-6,7-dichlorophthalazine

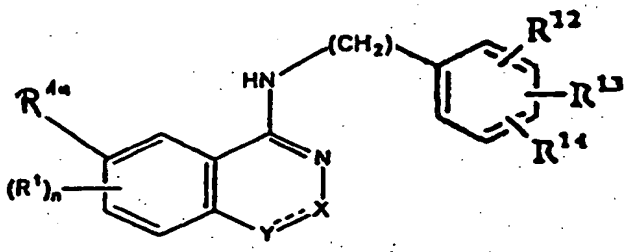
[0216]



[0217] In a similar manner to that of Example 40, the title compound was prepared from the compound prepared in Example 59
M.p.: 268-273 (dec.) °C
MASS: 495 (MH+)
1H-NMR (400 MHz, DMSO-d6) δ: 1.80-1.90(2H, m), 1.93-2.00(2H, m), 2.40-2.50(1H, m), 3.84-3.91(2H, m), 3.30-3.45 (2H, m), 3.82(3H, s), 4.62(2H, d, J=5.5Hz), 7.10(1H, d, J=8.5Hz), 7.34(1H, dd, J=8.5, 2.0Hz), 7.44(1H, d, J=2.0Hz), 7.85(1H, t, J=5.5Hz), 8.05(1H, s), 8.68(1H, s)

Claims

1. A fused pyridazine compound represented by the general formula (I) or a pharmacologically acceptable salt thereof:



(I)

wherein

n is an integer of 1 to 3;
R^1 represents a hydrogen atom, a halogen atom, a nitro group, an amino group, a cyano group or a 4-hydroxypiperidin-l-yl group; R^{1a} represents a halogen atom, a nitro group, an amino group, a cyano group or a 4-hydroxypiperidin-1 yl group;
R^{12}, R^{13} and R^{14} represent each independently hydrogen, halogen, optionally substituted lower alkyl or optionally substituted lower alkoxy, or alternatively two of R^{12}, R^{13} and R^{14} which are bonded to the carbon atoms adjacent to each other may be united to form methylenedioxy or ethylenedioxy) ;
--- represents a single bond or a double bond, and

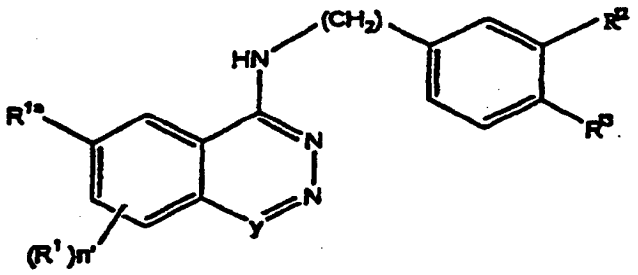
(1) when the above bond is a double bond;
then X represents a nitrogen atom, and Y represents a =C-B group, wherein B represents a halogen

atom, a group represented by the formula NR^7R^8, wherein R^7 represents hydrogen, or lower alkyl and R^8 represents lower alkyl optionally substituted by hydroxy, carboxy or pyridyl, or alternatively R^7 and R^8 together with the nitrogen atom to which they are bound to form a ring which may be substituted; a lower alkoxy group or a lower hydroxyalkoxy group;

(2) when the above bond is a single bond,
then X represents a $>NR^6$ group, wherein R^6 represents hydrogen or lower alkyl optionally substituted by a hydroxyl group, a carboxyl group, an acyl group or a tetrahydropyranyl group; and

Y represents a carbonyl group; provided that B is not Cl, when R^1 is 7- or 8-nitro and R^{12} and R^{13} are 3,4-methylenedioxy and R^{14} is hydrogen.

2. A fused pyridazine compound according to claim 1 represented by the general formula (II) or a pharmacologically acceptable salt thereof:



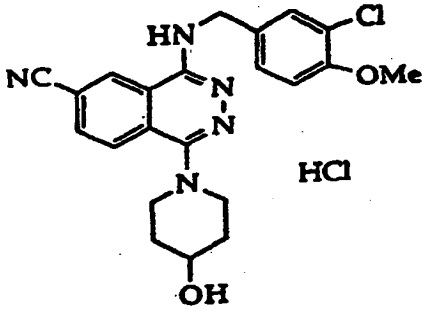
II

wherein

R^1,R1a, R^{12} and R^{13} are each as defined in claim 1;
y represents = C-B;
wherein B is as defined in claim 1; and
n' is an integer of 1 to 3.

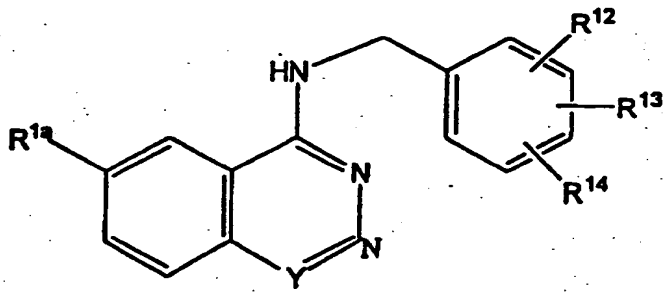
3. A fused pyridazine compound according to claim 2 or physiologically acceptable salt thereof wherein B is $-NR^7R^8$ and R^1 is hydrogen.

4. A fused pyridazine compound according to claim 3 or physiologically acceptable salt thereof represented by the following formula:



HCl

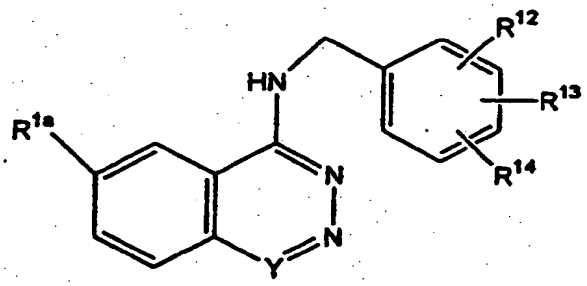
5. A fused pyridazine cornpound according to claim 1 represented by the general formula (V) or a pharmacologically acceptable salt thereof:



V

(wherein R^{1a} and y are each as defined above; and R^{12}, R^{13}, and R^{14} represent each independently halogen, methoxy or ethoxy).

6. A fused pyridazine compound according to claim 1 represented by the general formula (VI) or a pharmacologically acceptable salt thereof:



VI

(wherein R^{1a} and y are each as defined above; and R^{12}, R^{13} and R^{14} represent each independently hydrogen, methoxy or ethoxy.

7. Use of a fused pyridazine compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment or prophylaxis of pulmonary hypertension.

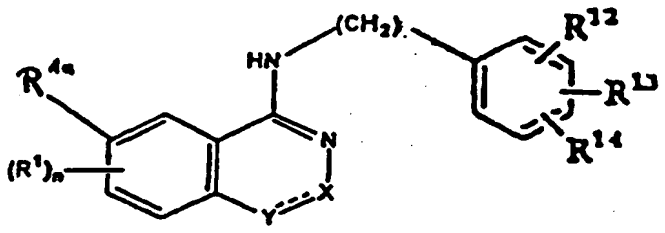
8. Use of a fused pyridazine compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment or prophylaxis of angina pectoris.

9. Use of a fused pyridazine compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment or prophylaxis of diseases for which a cyclic GMP phoshodiesterase inhibiting action is efficacious.

10. Use of a fused pyridazine compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment or prophylaxis of diseases for which an antiplatelet action is efficacious.

Patentansprüche

1. Kondensierte Pyridazin-Verbindung, angegeben durch die allgemeine Formel (I) oder ein pharmakologisch annehmbares Salz davon:



(I)

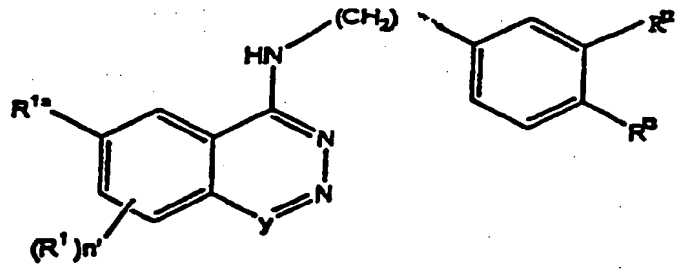
in der

n eine ganze Zahl von 1 bis 3 ist;
R^1 ein Wasserstoffatom, ein Halogenatom, eine Nitrogruppe, eine Aminogruppe, eine Cyanogruppe oder eine 4-Hydroxypiperidin-1-yl-Gruppe bedeutet;
R^{1a} ein Halogenatom, eine Nitrogruppe, eine Aminogruppe, eine Cyanogruppe oder eine 4-Hydroxypiperidin-1-yl-Gruppe bedeutet;
R^{12}, R^{13} und R^{14} jeweils unabhängig Wasserstoff, Halogen, gegebenenfalls substituiertes niederes Alkyl oder gegebenenfalls substituiertes niederes Alkoxy bedeuten, oder alternativ zwei von R^{12}, R^{13} und R^{14}, die an die benachbarten Kohlenstoffatome gebunden sind, verbunden sein können unter Bildung von Methylendioxy oder Ethylendioxy;
---- eine Einfachbindung oder eine Doppelbindung bedeutet und

(1) wenn die oben angegebene Bindung eine Doppelbindung ist, X ein Stickstoffatom bedeutet und Y eine =C-B-Gruppe, in der B ein Halogenatom, eine Gruppe, angegeben durch die Formel NR^7R^8, wobei R^7 Wasserstoff oder niederes Alkyl und R^8 niederes Alkyl ist, das gegebenenfalls durch Hydroxy, Carboxy oder Pyridyl substituiert ist, oder alternativ R^7 und R^8 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Ring bilden, der substituiert sein kann; eine niedere Alkoxygruppe oder eine niedere Hydroxy-alkoxy-Gruppe bedeutet;
(2) wenn die oben angegebene Bindung eine Einfachbindung ist,
X eine $>NR^6$-Gruppe bedeutet, wobei R^6 Wasserstoff oder niederes Alkyl ist, das gegebenenfalls durch eine Hydroxylgruppe, eine Carboxylgruppe, eine Acylgruppe oder eine Tetrahydropyranyl-Gruppe substituiert ist; und

Y eine Carbonylgruppe bedeutet; mit der Maßgabe, daß B nicht Cl ist, wenn R^1 7- oder 8-Nitro ist und R^{12} und R^{13} 3,4-Methylendioxy sind und R^{14} Wasserstoff ist.

2. Kondensierte Pyridazin-Verbindung nach Anspruch 1, angegeben durch die allgemeine Formel (II) oder ein pharmakologisch annehmbares Salz davon:



II

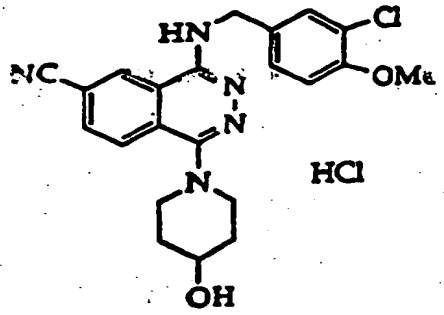
in der

R^1, R^{1a}, R^{12} und R^{13} jeweils wie in Anspruch 1 definiert sind,
Y =C-B bedeutet,

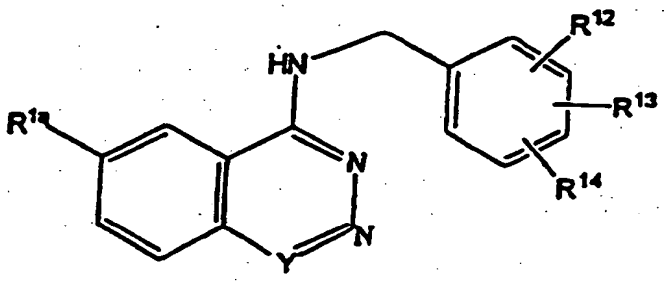
wobei B wie in Anspruch 1 definiert ist, und
n' eine ganze Zahl von 1 bis 3 ist.

3. Kondensierte Pyridazin-Verbindung nach Anspruch 2, oder ein physiologisch annehmbares Salz davon: wobei B $-NR^7R^8$ ist und R^1 Wasserstoff ist.

4. Kondensierte Pyridazin-Verbindung nach Anspruch 3 oder ein physiologisch annehmbares Salz davon, angegeben durch die folgende Formel:



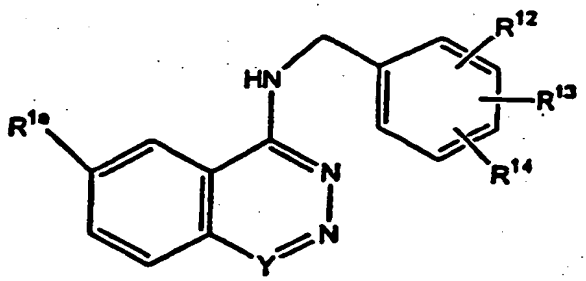
5. Kondensierte Pyridazin-Verbindung nach Anspruch 1, angegeben durch die allgemeine Formel (V) oder ein pharmakologisch annehmbares Salz davon:



V

(wobei R^{1a} und Y jeweils wie in Anspruch 1 definiert sind und R^{12}, R^{13} und R^{14} jeweils unabhängig Halogen, Methoxy oder Ethoxy bedeuten).

6. Kondensierte Pyridazin-Verbindung nach Anspruch 1, angegeben durch die allgemeine Formel (VI) oder ein pharmakologisch annehmbares Salz davon:



VI

(wobei R^{1a} und Y jeweils wie oben definiert sind und R^{12}, R^{13} und R^{14} jeweils unabhängig Wasserstoff,

Methoxy oder Ethoxy bedeuten).

7. Verwendung einer kondensierten Pyridazin-Verbindung nach einem der Ansprüche 1 bis 6 zur Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von pulmonarer Hypertension.

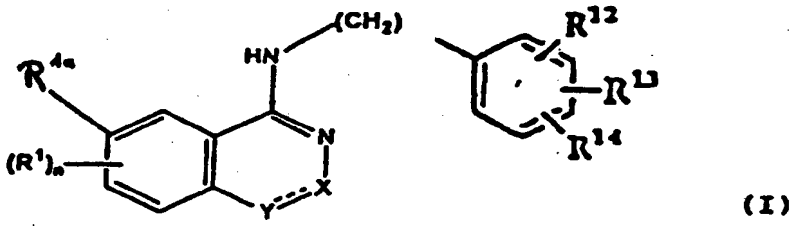
8. Verwendung einer kondensierten Pyridazin-Verbindung nach einem der Ansprüche 1 bis 6 zur Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von Angina pectoris.

9. Verwendung einer kondensierten Pyridazin-Verbindung nach einem der Ansprüche 1 bis 6 zur Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von Krankheiten, gegen die eine Hemmwirkung von cyclischer GMP Phosphodiesterase wirksam ist.

10. Verwendung einer kondensierten Pyridazin-Verbindung nach einem der Ansprüche 1 bis 6 zur Herstellung eines Arzneimittels zur Behandlung oder Prophylaxe von Krankheiten gegen die eine Anti-Thrombozyten-Wirkung wirksam ist..

Revendications

1. Composé de pyridazine condensé, représenté par la formule générale (I), ou sel pharmacologiquement acceptable de celui-ci :



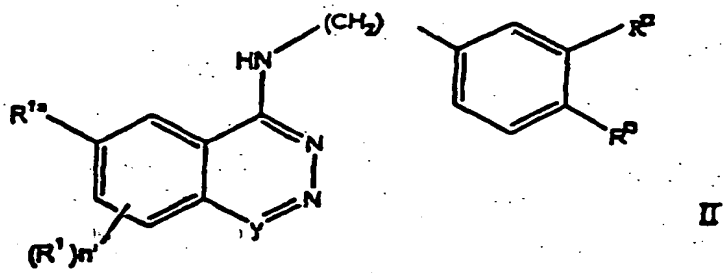
(I)

où

n est un entier compris entre 1 et 3 ;
R^1 représente un atome d'hydrogène, un atome d'halogène, un groupe nitro, un groupe amino, un groupe cyano ou un groupe 4-hydroxypipéridine-1-yl ;
R^{1a} représente un atome d'halogène, un groupe nitro, un groupe amino, un groupe cyano ou un groupe 4-hydroxypipéridine-1-yl ;
R^{12}, R^{13} et R^{14} représentent chacun indépendamment l'hydrogène, un halogène, un alkyl inférieur éventuellement substitué ou un alcoxy inférieur éventuellement substitué, ou en variante deux de R^{12}, R^{13} et R^{14} qui sont liés à des atomes de carbone voisins les uns des autres, peuvent être réunis pour former un méthylènedioxy ou un éthylènedioxy ;
--- représente une simple liaison ou une double liaison ; et

(1) quand la liaison ci-dessus est une double liaison, alors X représente un atome d'azote, et Y représente un groupe =C-B,
où B représente un atome d'halogène, un groupe représenté par la formule NR^7R^8, où R^7 représente l'hydrogène ou un alkyl inférieur et R^8 représente un alkyl inférieur éventuellement substitué par hydroxy, carboxy ou pyridyle, ou en variante R^7 et R^8 forment, avec l'atome d'azote auquel ils sont liés, un anneau qui peut être substitué; un groupe alcoxy inférieur ou un groupe hydraoxyalcoxy inférieur ;
(2) quand la liaison ci-dessus est une simple liaison, alors X représente un groupe NR^6, où R^6 représente l'hydrogène ou un alkyl inférieur éventuellement substitué par un groupe hydroxyl, un groupe carboxyl, un groupe acyl ou un groupe tétrahydropyranyl, et Y représente un groupe carbonyl ;
à condition que B ne soit pas Cl quand R^1 est 7- ou 8-nitro et R^{12} e R^{13} sont 3,4-méthylènedioxy et R^{14} est l'hydrogène.

2. Composé de pyridazine condensé selon la revendication 1, représenté par la formule générale (II) ou sel pharmacologiquement acceptable de celui-ci :



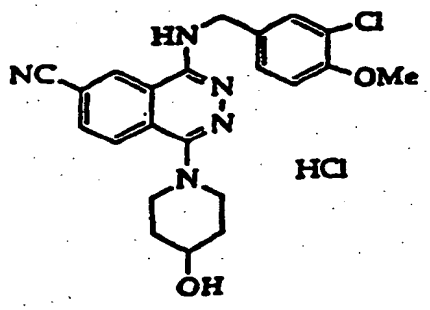
II

où

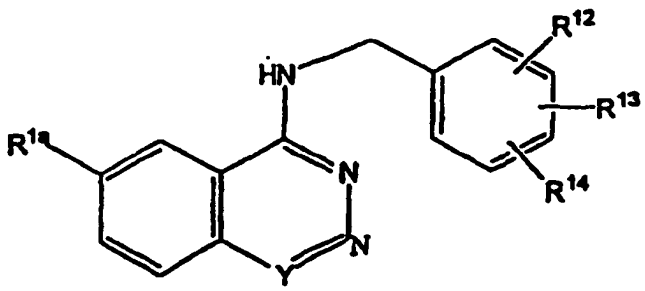
R^1, R^{1a}, R^{12} et R^{13} sont définis à la revendication 1 ;
y représente =C-B,
où B est défini à la revendication 1, et
n' est un entier compris entre 1 et 3.

3. Composé de pyridazine condensé selon la revendication 2, ou sel pharmacologiquement acceptable de celui-ci, dans lequel B est $-NR^7R^8$ et R_1 est l'hydrogène.

4. Composé de pyridazine condensé selon la revendication 3, ou sel pharmacologiquement acceptable de celui-ci, représenté par la formule générale :



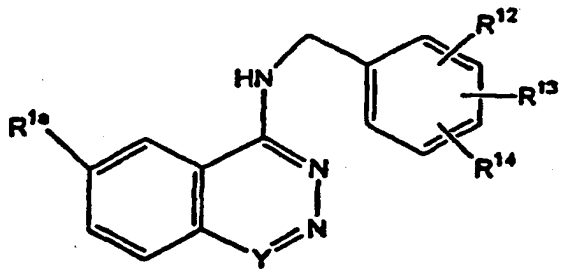
5. Composé de pyridazine condensé selon la revendication 1 représenté par la formule générale (V), ou sel pharmacologiquement acceptable de celui-ci:



V

(où R^{1a} et y sont tels que définis ci-dessus ; et R^{12}, R^{13} et R^{14} représentent chacun indépendamment un halogène, méthoxy ou éthoxy).

6. Composé de pyridazine condensé selon la revendication 1 représenté par la formule générale (VI), ou sel pharmacologiquement acceptable de celui-ci :



VI

(où R^{1a} et y sont tels que définis ci-dessus ; et R^{12}, R^{13} et R^{14} représentent chacun indépendamment l'hydrogène, méthoxy ou éthoxy).

7. Utilisation d'un composé de pyridazine condensé selon l'une quelconque des revendications 1 à 6 dans la fabrication d'un médicament destiné au traitement ou à la prévention de l'hypertension pulmonaire.

8. Utilisation d'un composé de pyridazine condensé selon l'une quelconque des revendications 1 à 6 dans la fabrication d'un médicament destiné au traitement ou à la prévention de l'angine de poitrine.

9. Utilisation d'un composé de pyridazine condensé selon l'une quelconque des revendications 1 à 6 dans la fabrication d'un médicament destiné au traitement ou à la prévention de maladies pour lesquels une action d'inhibition cyclique de la phosphodiestérase GMP est efficace.

10. Utilisation d'un composé de pyridazine condensé selon l'une quelconque des revendications 1 à 6 dans la fabrication d'un médicament destiné au traitement ou à la prévention de maladies pour lesquelles une action antiplaquettes est efficace.